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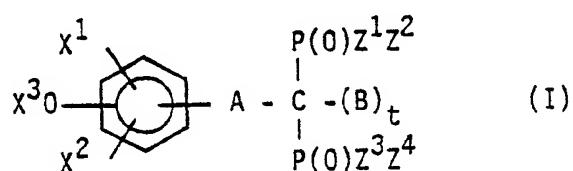
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㉓ Phenol substituted gem-diphosphonate derivatives, process for their preparation and pharmaceutical compositions containing them.

㉔ The invention relates to new gem-diphosphonates derivatives substituted by phenol groups of formula (I):



as well as the process for their preparation and the pharmaceutical compositions containing them.

EP 0 339 237 A2

PHENOL SUBSTITUTED GEM-DIPHOSPHONATE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This invention relates to a novel class of compounds, phenol substituted gem-diphosphonate derivatives as well as the process for preparing such compounds. It further relates to pharmaceutical compositions containing the above-mentioned compounds especially for the treatment of hyperlipidemia.

Many epidemiologic studies have shown that people with high levels of serum cholesterol are at high risk of developing coronary artery diseases. The convincing and definitive evidence that lowering serum cholesterol with the aid of hypocholesterolemic drugs reduces the risk of coronary heart diseases was provided by the Lipid Research Clinics Coronary Primary Prevention Trial reports (The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. Journal of the American Medical Association 251, p.351-364, 1984. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. Journal of the American Medical Association 251, p. 365-374, 1984).

In addition, the most recent report from the Helsinki study showed that gemfibrozil treatment, which was associated with the modification of the serum lipoprotein levels and decreased plasma triglycerides, reduces the incidence of coronary heart disease in men with dyslipidemia (The New England Journal of Medicine 317 (20), p. 1237-1245, 1987).

The phenol substituted gem-diphosphonates were tested and discovered to be potent hypolipidemic and lipid altering agents, in addition some were found to possess hypotensive activity. These gem-diphosphonates were therefore potentially useful agents for the treatment of dyslipemias and associated cardiovascular diseases.

H. Gross and coworkers have described the synthesis of (3,5-ditertiobutyl-4-hydroxyphenyl)methylidene diphosphonic acid and its Me, Et and Pr esters in Journal f. prakt. Chemie 317(6), p. 890-896 (1975); ibid. 318(3), p. 403-408 (1976) and ibid. 320(2), p. 344-350 (1978). No potential application of these compounds was provided in the description.

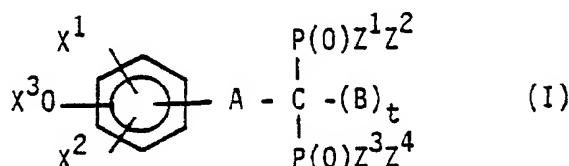
W. Lehnert reported in Tetrahedron 30, p. 301-305 (1974) a method for the preparation of simple phenylethylenylidene-diphosphonate and-carboxyphosphonate esters, without any information on their potential application.

The US Patent No. 4,696,920 (1987) of Symphar S.A. reports the preparation of tetraethyl and tetrabutyl 2-(3,5-ditertiobutyl-4-hydroxy)benzyl-1,3-propylidenediphosphonate and their possible use in the treatment of cardiovascular diseases induced by or associated with the dysfunction of the slow calcium channels.

The UK patent 2 043 072 (1979) of Symphar S.A. discloses the synthesis of unsubstituted phenyl- and phenoxy-alkylidene-1,1-diphosphonic acids and Me and Et esters and their application as antiatherosclerotic agents.

The present invention relates to compounds of formula (I):

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where:

- Z¹, Z², Z³ and Z⁴ identical or different are
- OR where R is H, a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms,
- OM where M is an alkaline or alkaline earth metal ion or an ammonium group NR₄ where R has the same meaning as defined above,
- NR₂ where R has the same meaning as defined above,
- Z¹, Z² and Z³, Z⁴ may form an alkylidenedioxy ring comprising 2 to 8 carbon atoms.
- X¹, X² identical or different, are H, a halogen atom, a straight, branched or cyclic alkyl or alkoxy group from 1 to 8 carbon atoms,
- X³ is H, an alkyl group R¹ from 1 to 4 carbon atoms, an acyl group C(O)R¹, a carbamyl group C(O)NHR¹ where R¹ is described as above; X³O and one of the two other substituents X¹ or X² may form an

alkylidenedioxy ring comprising from 1 to 4 carbon atoms,

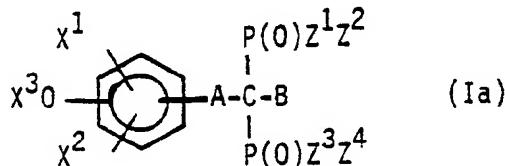
- A is $-\text{CH}=\text{CH}-\text{CH}_2-$, $-(\text{CH}_2)_n-$, $-\text{O}(\text{CH}_2)_n-$, $-\text{S}-$, SO_2 , $-\text{S}(\text{CH}_2)_n-$, $-\text{SO}_2(\text{CH}_2)_n-$, where n is an integer from 1 to 7, $-(\text{CH}=\text{CH})_k-(\text{CH}_2)_d-\text{CH}=$ where k is zero or 1 and d is an integer from zero to 4,

- B is H, an alkyl group from 1 to 4 carbon atoms,

5 - t is zero or 1, with the proviso that t is zero only when A is $(\text{CH}=\text{CH})_k-(\text{CH}_2)_d-\text{CH}=$ where k and d are as described above.

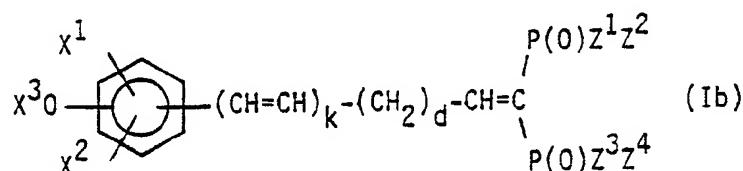
The compounds of formula (I) include the phenol substituted alkylidenediphosphonates (Ia) and the phenol substituted alkenylidenediphosphonates (Ib)

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25 where X¹, X², X³, A, B, k, d, Z¹, Z², Z³, Z⁴ are as described above.

Compounds of structure (Ia) include, for example, those in which:

- X¹, X² identical or different are alkyl groups from 1 to 8 carbon atoms,

- X³ is hydrogen,

- A is $\text{CH}=\text{CH}-\text{CH}_2$, $(\text{CH}_2)_n$, S, SO_2 , $\text{S}(\text{CH}_2)_n$, $\text{SO}_2(\text{CH}_2)_n$, where n is 1-7,

30 - B is hydrogen or a C₁-C₄ alkyl group,

- Z¹, Z², Z³, Z⁴ identical or different are OH, alkoxy groups of 1 to 8 carbon atoms or one or both of the pairs Z¹, Z² and Z³, Z⁴ are an alkylidenedioxy group of 2 to 8 carbon atoms.

Compounds of structure (Ib) include, for example, those in which

- X¹, X² identical or different are alkyl groups from 1 to 8 carbon atoms,

35 - X³ is hydrogen,

- k is zero or 1 and d is zero to 4,

- Z¹, Z², Z³, Z⁴ identical or different are OH, alkoxy groups of 1 to 8 carbon atoms or one or both of the pairs Z¹, Z² and Z³, Z⁴ are an alkylidenedioxy group of 2 to 8 carbon atoms.

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PROCESS FOR PREPARING COMPOUNDS OF FORMULA (I)

The present invention also relates to a process for preparing gem-diphosphonates of formula (Ia) and (Ib).

45 The experimental procedure for preparing (Ia) consists in reacting the diphosphonate compound III with a base such as sodium hydride, sodium metal, sodium alkoxide, n-butyl lithium or lithium diisopropylamide. The starting product II is then reacted with the anion of compound III thus formed in situ to give the substituted diphosphonate (Ia). The reaction takes place in solvents such as hexane, heptane, benzene, toluene, tetrahydrofuran, dioxane, dimethoxyethane, methyl tertiobutyl ether or N, N-dimethylformamide.

50 The solvents can be utilized pure or as a mixture, depending on the solvent polarity desired. The temperature range of the reaction is between -78 °C and the boiling point of the solvent or solvent mixture. The reaction time varies between several hours and several days. In the case where A is a sulfur atom, the appropriate starting compound II is the bis (substituted phenol) disulfide and the preferred base is n-butyl lithium.

55 The procedure for preparing (Ib) consists in condensing the appropriate aldehyde IV with the diphosphonate compound V using titanium tetrachloride and a tertiary amine such as methyl morpholine or pyridine as catalysts. The reaction is carried out in an ether solvent such as tetrahydrofuran, dioxane or dimethoxyethane. The polarity of the reaction medium can be conveniently modified by adding a non-polar

solvent such as tetrachloromethane. The temperature of the reaction varies between -15 ° C and 40 ° C, preferably between 0 ° C and 30 ° C.

The obtained alkenyldene-diphosphonates (Ib) can be hydrogenated to the corresponding alkylidene-diphosphonates (Ia) where B = H. In the particular case where structure (Ib) contains two double bonds, i.e. 5 when k = 1, the reduction conditions can be made to form either of the following two compounds (Ia): the partially saturated compound where A = (CH = CH)_k-(CH₂)_d-CH₂, B = H, or the completely saturated compound where A = (CH₂-CH₂)_k-(CH₂)_d-CH₂, B = H.

The partially saturated compound (Ia) where A = (CH = CH)_k-(CH₂)_d-CH₂, B = H, can be made predominantly when (Ib), where k = 1, is reduced with a complex hydride reagent such as sodium borohydride or 10 lithium borohydride in a polar solvent which can be methanol, ethanol at a temperature between -15 ° and room temperature.

The completely saturated compound (Ia) where A = (CH₂CH₂)_k-(CH₂)_d-CH₂, B = H, can be obtained from 15 (Ib), where k = 1, by reduction with an excess of complex hydride reagent such as sodium borohydride or lithium borohydride in methanol or ethanol as solvent at a temperature between room and reflux temperature. Another convenient reduction method is the catalytic hydrogenation using palladium or platinum adsorbed on active charcoal as catalyst. Suitable solvents include methanol, ethanol, dimethoxyethane, dioxane, tetrahydrofuran and acetic acid. The reduction is performed at room temperature and at a pressure between 1 and 4 atm.

Compounds (I) obtained through one of the procedures described in page 8 can be derivatized into 20 other products with different ester groups. One such method involves the hydrolysis of the tetraethyl ester compounds (I), Z¹-Z⁴ = OEt, with hydrochloric acid or bromotrimethylsilane/water to yield the corresponding diphosphonic acids (I), Z¹-Z⁴ = OH. The latter compounds are alkylated by using trialkyl orthoformates to 25 form the corresponding tetraalkyl esters. An alternative method consists in reacting the tetraethyl ester derivative with bromotrimethylsilane/phosphorus pentachloride to form the diphosphonyl tetrachloride. The esterification of this intermediate with various alcohols or diols yields new derivatives (I) where the pairs of substituents Z¹, Z² and Z³, Z⁴ may be individual alkoxy groups or may form alkylidenedioxy groups.

The above described synthetic procedures are described on pages 8 and 9.

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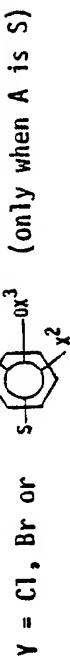
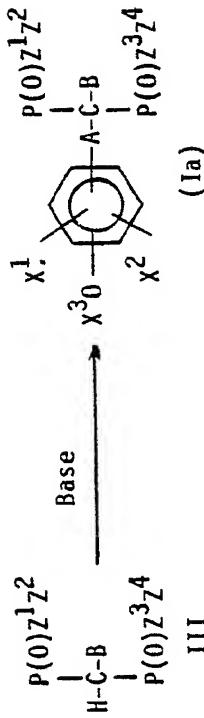
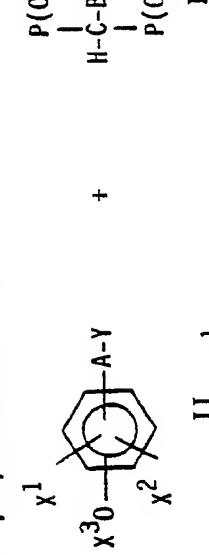
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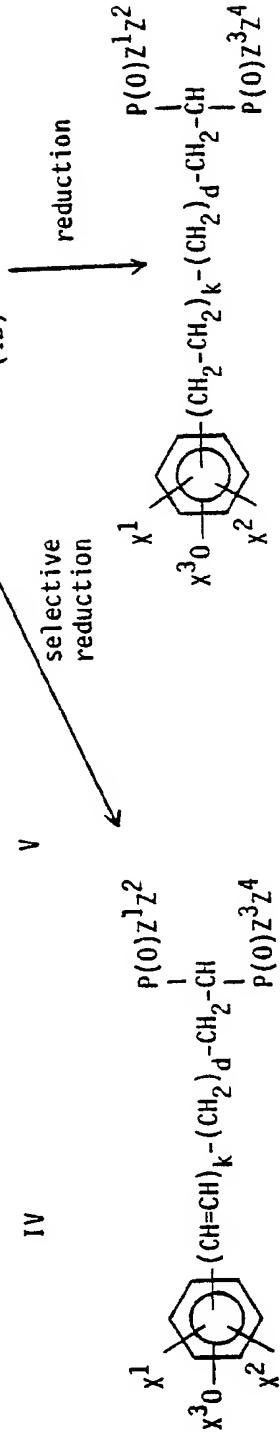
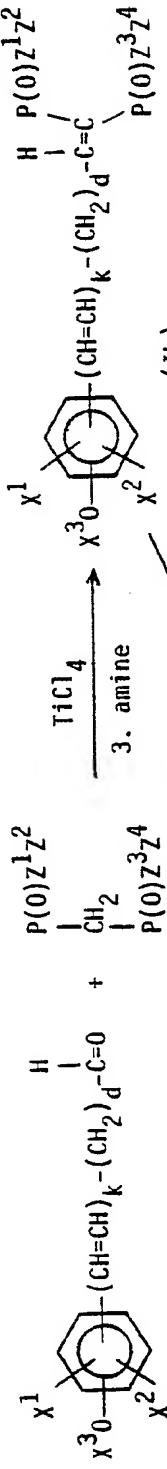
55 50 45 40 35 30 25 20 15 10 5

SYNTHETIC PROCEDURE

- General preparation of (Ia)



- Preparation of (Ib) and (Ia) when B = H and A = $(\text{CH}=\text{CH})_k-(\text{CH}_2)_d-\text{CH}_2$ and $(\text{CH}_2\text{CH}_2)_k-(\text{CH}_2)_d-\text{CH}_2$ where k = zero or 1 and d = zero to 4



(Ia), B=H, A=(CH2-CH2)k-(CH2)d-CH2

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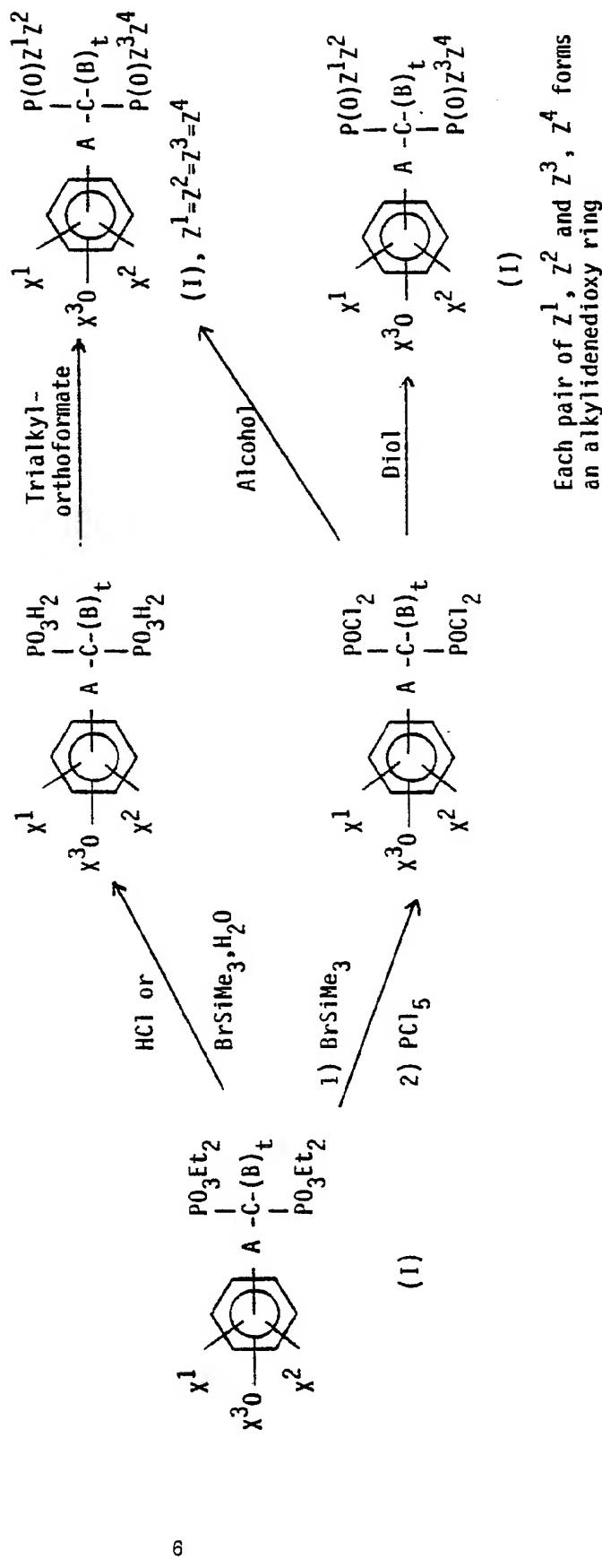
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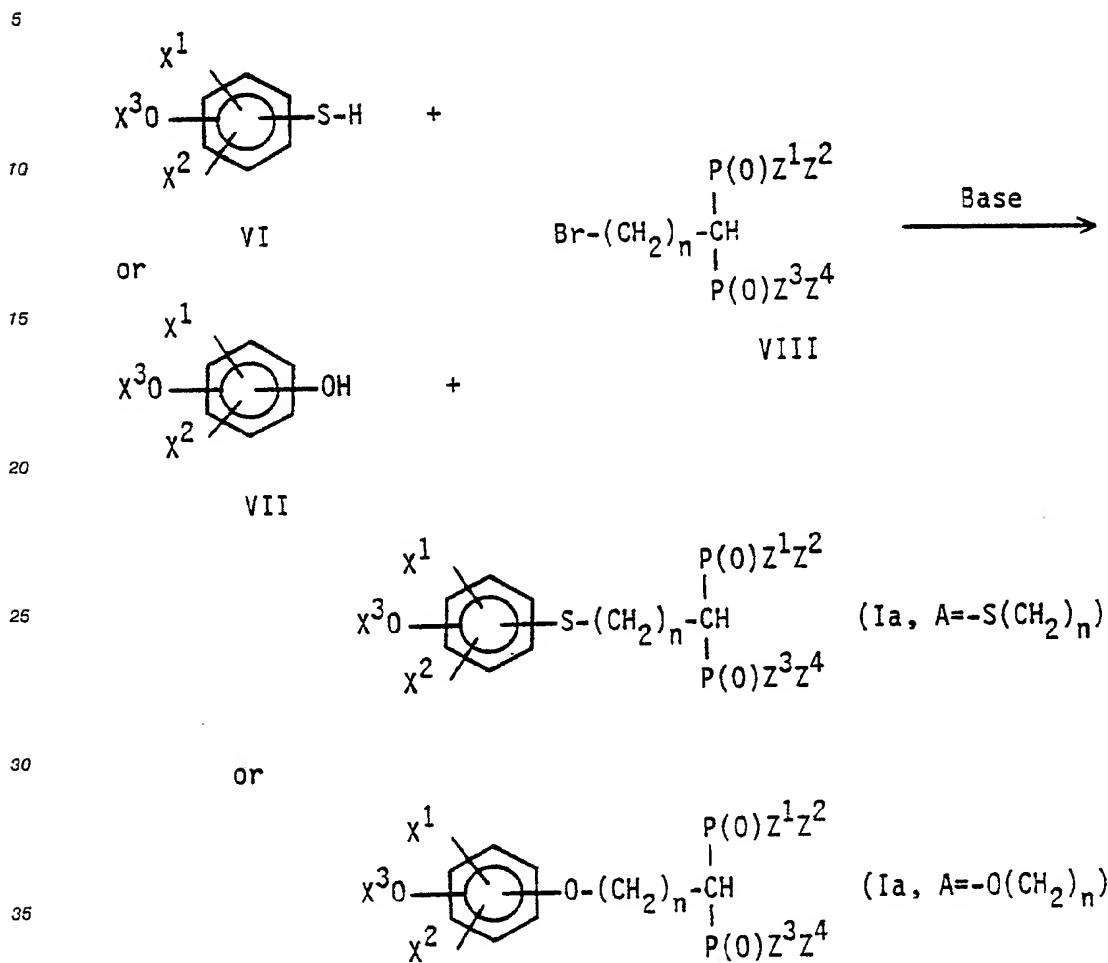
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SYNTHETIC PROCEDURE (cont.)

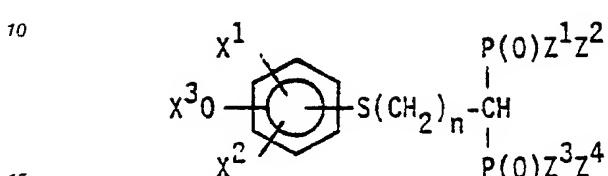
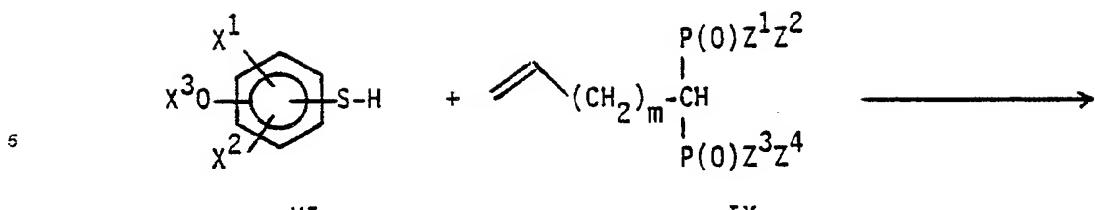


Each pair of Z^1 , Z^2 and Z^3 , Z^4 forms
an alkylidenedioxy ring

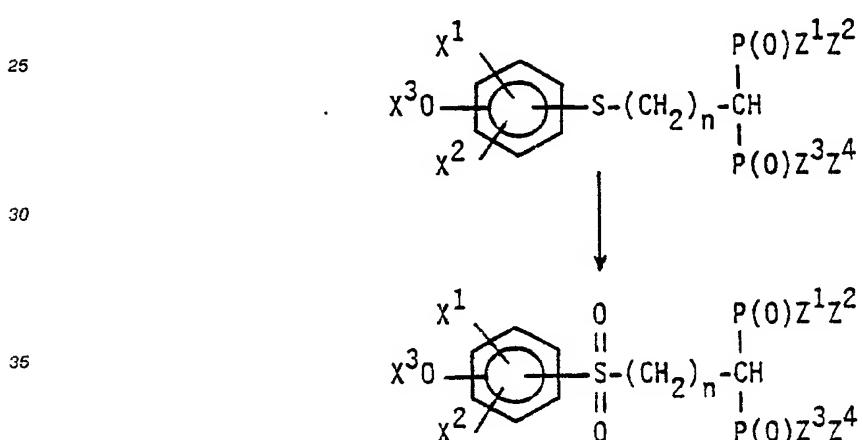
When A is $S-(CH_2)_n$ or $O-(CH_2)_n$, (Ia) can also be prepared by reacting bromoalkylenediphosphonate VIII with respectively the thiohydroquinone VI or hydroquinone derivative VII in presence of a base.



When A is $S-(CH_2)_n$ where $n \geq 3$, one additional method for preparing (Ia) involves reacting VI with an 40 alkenylenediphosphonate IX in presence of a radical initiating agent such as benzoyl peroxide or hydrogen peroxide.



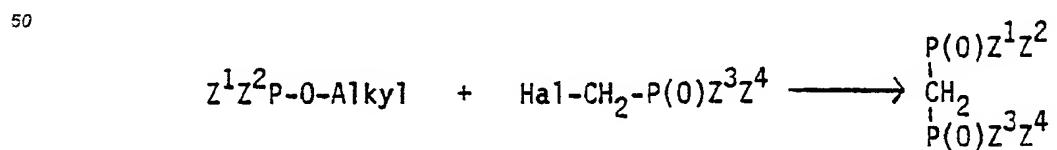
20 The sulfide group is converted to the higher oxidation states, namely the sulfone groups, by using an oxidative agent which may be a peracid such as m-chloroperbenzoic acid or a peroxide salt such as potassium permanganate or potassium hydrogen persulfate.



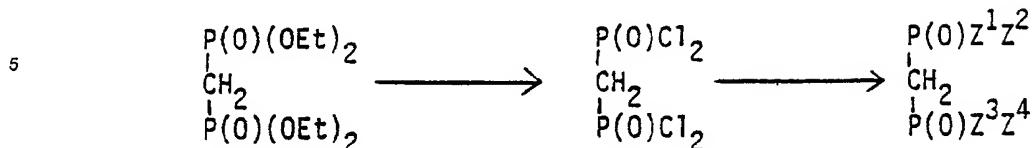
40 Compounds (I) where X^3 is different from H can be prepared by using the corresponding starting compound II where $X^3 \neq H$. One alternative method involves derivatizing the phenolic -OH group in compounds (I) by standard synthetic procedures: alkylation, by reacting the phenoxide anion with alkylating reagents such as alkyl halide or dialkyl sulfate, esterification by using acylating reagents such as acid anhydrides or acyl halides to form the corresponding esters or by using isocyanates to form the corresponding carbamates.

The starting compounds V which are not commercially available are prepared by one of the two following methods.

- Arbuzov reaction between an alkyl phosphite and a halogenomethylphosphonate



- Transesterification of the methylenediphosphonate ethyl ester



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V

These two methods provide new starting compounds V where the substituents Z^1 , Z^2 , Z^3 , and Z^4 may be individual alkoxy groups or where the pairs of substituents Z^1 , Z^2 and/or Z^3 , Z^4 may form alkylidenedioxy rings.

15 The structures of compounds of formula (I) are determined by elemental analysis, infrared (IR), mass (MS) and nuclear magnetic resonance (NMR) spectroscopies. The purity of the compounds is verified by thin layer chromatography (Silicagel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ or $\text{CHCl}_3/\text{MeOH}$ eluent mixtures), gas liquid chromatography (Methyl silicone column) or high performance liquid chromatography (Octadecylsilane C_{18} reversed phase column).

20 The abbreviations used in this patent application are as follows:

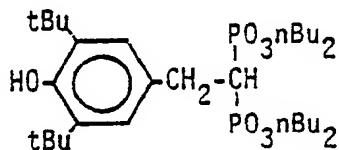
In tables 1 and 2, n- is normal, i- is iso-, sec is secondary-, t is tertio-. In the NMR spectra, s is singlet, d is doublet, t is triplet, m is multiplet. The temperatures are measured in degree Celsius and the melting points are uncorrected. The boiling points refer to values obtained by short path distillation carried out in a ball tube type distillation apparatus (Kugelrohr).

25 The present invention will be further described by the examples 1 to 23 which are typical of the synthetic procedures used.

30 Example 1 (Compound 7)

Tetrabutyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate

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A solution of 3,5-ditertiobutyl-4-hydroxybenzyl bromide (2.48 g, 8.3 mmol) in 30 ml dioxane was added to a solution of 12.5 mmol of sodium tetrabutyl methylenediphosphonate prepared by reacting an equimolar amount of NaH and tetrabutyl methylenediphosphonate in 30 ml tetrahydrofuran. The reaction mixture was 45 refluxed for 16 h then was partitioned between H_2O and CHCl_3 . The dried organic phase (MgSO_4) was evaporated and the residue was purified by column chromatography (SiO_2 , CHCl_3 then 95/5 $\text{CHCl}_3/\text{MeOH}$) to afford 2.9 g (4.6 mmol, 56%) of tetrabutyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate.

IR (film):
 50 2980 cm^{-1} : aliphatic C-H
 1440: t-C₄H₉
 1240: P=O
 1020-970 : P-O-C
 NMR (CDCl_3):
 55 δ =
 7.05 (s, 2H): aromatic H
 5.08 (s, 1H) OH
 4.1-3.95 (m, 8H): P-O-CH₂-C₃H₇

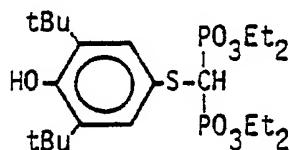
3.18 (t x d, $J = 7$ and 16 Hz, 2H): Ph-CH₂-
 2.66 (t x t, $J = 7$ and 24 Hz, 1H): Ph-CH₂-CH
 1.60 (sextet, $J = 7$ Hz, 8H): P-O-CH₂CH₂-C₂H₅
 1.44 (s, 18H): t-C₄H₉
 5 1.38 (multiplet, $J = 7$ Hz, 8H): P-O-C₂H₄-CH₂-CH₃
 0.90 (2 x t, $J = 7$ Hz, 12H): P-O-C₃H₆-CH₃

10 Example 2 (Compound 5)

Tetraethyl 3,5-ditertiobutyl-4-hydroxyphenylthio-methylenediphosphonate

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To a solution of tetraethyl methylenediphosphonate (2.43 g, 8.43 mmol) in 15 ml dry tetrahydrofuran were added 5.3 ml (8.43 mmol) of 1.6 M n-butyllithium in hexane at -78 °C under nitrogen. To the above 25 solution were then added 15 ml of a tetrahydrofuran solution of 4.0 g (8.43 mmol) of bis(3,5-ditertiobutyl-4-hydroxyphenyl) disulfide, prepared according to T. Fujisawa et al., *Synthesis* 1972, p. 624-625. The mixture was maintained at -78 °C for 1 h and then stirred at 25 °C for 3 days. Hydrolysis was performed with 20 ml saturated NH₄Cl solution and the mixture was extracted with 3 x 40 ml diethyl ether. The organic phase was dried over MgSO₄, evaporated and the residue was purified by column chromatography (SiO₂, 95/5 CH₂Cl₂/MeOH). It was obtained 2.2g (4.2 mmol) of a yellow oil which slowly crystallized; yield = 49%.
 30 mp = 78-80 °C

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Elemental analysis C ₂₃ H ₄₂ O ₇ P ₂ S									
	% calc.	C	52.66	H	8.07	P	11.88	S	6.11
	% found	C	52.13	H	7.77	P	11.65	S	6.62

40 IR (film):

3600 + 3450 cm⁻¹: OH

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1430: t-C₄H₉

1250: P=O

1040: P-O-C

NMR (CDCl₃):

δ =

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7.5 (s, 2H): aromatic H

5.4 (s, 1H): OH

4.35-4.2 (m, 8H): P-O-CH₂CH₃

3.55 (t, $J = 21$ Hz, 1H): -CH-PO₃Et₂

1.45 (s, 18H): t-C₄H₉

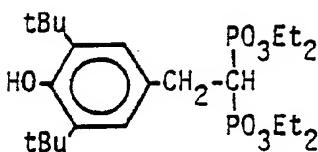
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1.35 (t, $J = 7$ Hz, 12H): P-O-CH₂-CH₃

MS: 524 (M⁺)

55 Example 3 (Compound 4)

Tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate



Tetraethyl methylenediphosphonate (21.2 g, 73.5 mmol) was added at room temperature to a 80% dispersion of sodium hydride in mineral oil (2.2 g, 73.5 mmol) suspended in 70 ml dry benzene. To this 10 solution of sodium tetraethyl methylenediphosphonate was then added a 30 ml toluene solution of 20 g (66.8 mmol) of 3,5-ditertiobutyl-4-hydroxybenzylbromide prepared according to H. Gross, H. Seibt and I. Keitel, *Journal für prakt. Chemie* 317 (6), p. 890-896 (1975). The resulting mixture was refluxed for 16 hours. The cooled toluene phase was extracted with H₂O, dried over MgSO₄ and evaporated to dryness. The 15 residue was purified by column chromatography (SiO₂, pure CHCl₃ followed by a 95/5 CHCl₃/MeOH solution) to give 21.3 g (63% yield) of tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate.
mp = 62-63 °C

20

Elemental analysis C ₂₄ H ₄₄ O ₇ P ₂						
	% calc.	C	56.90	H	8.76	P
	% found	C	56.76	H	8.53	P
					12.23	12.15

25 IR (KBr):

3400 cm⁻¹: O-H
2850: aliphatic C-H

1440: t-butyl

1240: P=O

1040: P-O-C

30 NMR (CDCl₃): δ =

7.1 (s, 2H): aromatic H

5.1 (s, 1H): OH

4.15 - 4.05 (m, 8H): P-O-CH₂CH₃35 3.18 (t x d, J = 6 and 17Hz, 2H): Ph-CH₂2.65 (t x t, J = 6 and 24Hz, 1H): Ph-CH₂-CH1.45 (s, 18H): tC₄H₉1.26 (two overlapping t, J = 7Hz, 12H): P-O-CH₂-CH₃

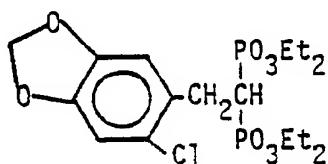
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Example 4 (Compound 13)

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Tetraethyl 2-(3,4-methylenedioxy-6-chlorophenyl)-ethylidene-1,1-diphosphonate

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To a solution of sodium tetraethyl methylenediphosphonate (22 mmol) in 15 ml dry dimethoxyethane 55 were added 4.1 g (20 mmol) of 6-chloropiperonyl chloride. After 16 h at reflux the reaction mixture was partitioned between Et₂O (3 x 20 ml) and H₂O (20 ml) and the organic phase was dried over MgSO₄. Short path distillation (Kugelrohr) gave 3.1 g (8.5 mmol, 43%) of the title compound.

bp = 200 °C/0.05 mmHg

IR (film)

2950 cm^{-1} : aliphatic C-H
 1240: P=O
 1030: P-O-C + OCH₂O

5

Elemental analysis: C ₁₇ H ₂₇ ClO ₈ P ₂								
% calc.	C	44.70	H	5.96	P	13.56	Cl	7.56
% found	C	44.51	H	6.21	P	13.41	Cl	7.65

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NMR (CDCl₃):

δ =

6.76 (s, 1H): aromatic H
 6.70 (s, 1H): aromatic H
 5.84 (s, 2H): O-CH₂-O
 4.10-3.96 (m, 8H): P-O-CH₂CH₃
 3.10-3.20 (m, 2H): Ph-CH₂
 2.80 (t x t, J = 7 and 24 Hz, 1H): Ph-CH₂CH
 1.12 (two overlapping t, J = 7 Hz, 12H): P-O-CH₂CH₃

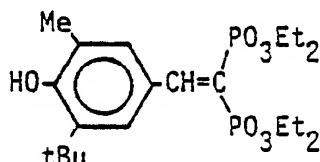
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Example 5 (Compound 30)

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Tetraethyl 2-(3-tertiobutyl-4-hydroxy-5-methylphenyl)-ethenylidene-1,1-diphosphonate

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35

Under nitrogen, 300 ml of dry tetrahydrofuran were placed in a 500 ml reactor and were cooled to 0°. Titanium tetrachloride (27.5 g, 145 mmol) was added dropwise followed by 10 g (52 mmol) of 3-tertiobutyl-4-hydroxy-5-methylbenzaldehyde synthesized according to G.A. Nikiforov et al, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk 1962, p. 1836-8; Chem. Abst. 58, 7856f (1963). Tetraethyl methylenediphosphonate (21 g, 72 mmol) was added followed by pyridine (22.9 g, 290 mmol). The mixture was stirred for 3 h at room temperature and concentrated under vacuum. The residue was partitioned between Et₂O and H₂O. The ether phase was washed with NaHCO₃ solution to pH 7, dried and evaporated to dryness. An amount of 18.5 g (40 mmol, 77% yield) was obtained of the title compound, pure by GLC.

40

IR (film):

3400 cm^{-1} : OH
 2950: aliphatic C-H

1240: P=O

1060: P-O-C

45

NMR (CDCl₃):

δ =

8.2 (d x d, J = 30 and 50Hz, 1H): Ph-CH=CP₂

7.7-7.6 (m, 2H): aromatic H

4.25-4.05 (m, 8H): P-O-CH₂CH₃

2.25 (s, 3H): CH₃

50

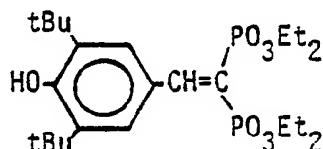
1.4 (s, 9H): t-C₄H₉

1.35 and 1.2 (2 x t, 12H): P-O-CH₂-CH₃

Example 6 (Compound 33)Tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate

5

10



An amount of 700 ml dry tetrahydrofuran was placed in a 1 l reactor under nitrogen atmosphere.
 15 Titanium tetrachloride (96.5 g, 0.51 mol) was added to the THF solution cooled to 0°, followed by 40.0 g (0.17 mol) 3,5-ditertiobutyl-4-hydroxybenzaldehyde. Tetraethyl methylenediphosphonate (69.1 g, 0.24 mol) was added dropwise, followed by methylmorpholine (97.6 g, 0.97 mol) and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was then partitioned between H₂O and diethyl ether. The ether phase was washed until neutral pH, dried and evaporated. The residue was recrystallized in acetone
 20 and the mother liquor purified by column chromatography (SiO₂, pure CHCl₃ followed by 95/5 CHCl₃/MeOH). The combined fractions gave 53 g (0.11 mol, 62% yield) of tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate.

mp = 120-121 °C

25

Elemental analysis C ₂₄ H ₄₂ O ₇ P ₂						
% calc.	C	57.14	H	8.39	P	12.28
% found	C	56.89	H	8.23	P	12.05

30 IR (KBr):

3200 cm⁻¹: OH

2850: aliphatic C-H

1570: C = C

1440: t-butyl

35 1240: P = O

1060: P-O-C

NMR (CDCl₃):

δ =

40 8.25 (d x d, J = 30 and 48 Hz, 1H): Ph-CH=C-P₂

7.7 (m, 2H): aromatic H

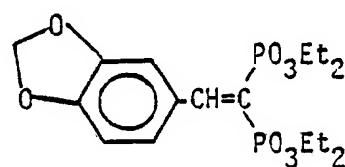
5.65 (s, 1H): OH

4.2 - 4.0 (2 x m, 8H): P-O-CH₂-CH₃1.5 and 1.45 (2 x s, 18H): t-C₄H₉45 1.4 and 1.2 (2 x t, 12H): P-O-CH₂CH₃Example 7 (Compound 38)

50

Tetraethyl 2-(3,4-methylenedioxyphenyl)-ethenylidene-1,1-diphosphonate

55



Under nitrogen, $TiCl_4$ (11 ml, 100 mmol) was added dropwise to a 200 ml solution of dry THF cooled to 0 °C. Sequentially were added piperonal (7.5 g, 50 mmol) dissolved in 30 ml THF, tetraethyl methylenediphosphonate (14.4 g, 50 mmol) and N-methylmorpholine (20.2 g, 200 mmol). The mixture was stirred at room temperature for 90 min, H_2O (50 ml) was added and the resulting mixture was extracted by Et₂O (3 x 100 ml). The residue of the organic phase was purified by column chromatography (SiO₂, 95/5 CHCl₃/MeOH) to give 13.7 g (32.6 mmol, 66%) of the title compound.

IR (film): 2980, 1560 (C = C), 1250 (P = O), 1030 (P-O-C)

10

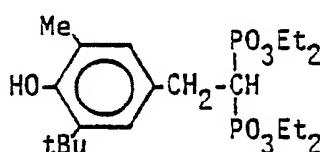
Elemental analysis: C ₁₇ H ₂₆ O ₈ P ₂						
% calc.	C	48.58	H	6.24	P	14.74
% found	C	48.20	H	6.01	P	14.21

15 NMR (CDCl₃):
 δ =
8.26-8.04 (dxd, J = 48 and 30 Hz, 1H): Ph-CH = C
7.52 (S, 1H): aromatic H
7.28 (d, 1H): aromatic H
6.80 (d, 1H): aromatic H
20 5.98 (S, 2H): O-CH₂-O
4.15 and 4.05 (two m, 8H): P-O-CH₂CH₃
1.30 and 1.16 (two t, 12H): P-O-CH₂CH₃

25 Example 8 (Compound 1)

30 Tetraethyl 2-(3-tertiobutyl-4-hydroxy-5-methylphenyl)-ethylenediene-1,1-diphosphonate

35



An amount of 11.4 g (24.6 mmol) of tetraethyl 2-(3-tertiobutyl-4-hydroxy-5-methylphenyl)-ethylenediene-1,1-diphosphonate was added to a solution of 4.65 g (123 mmol) NaBH₄ in EtOH and the mixture was refluxed for 90 min. The ethanol solution was evaporated and the residue was partitioned between 2.5N HCl and Et₂O. Evaporation of the dried organic phase gave an oil which was purified by short-path distillation. 9.9 g (87% yield) of tetraethyl 2-(3-tertiobutyl-4-hydroxy-5-methylphenyl)-ethylenediene-1,1-diphosphonate were obtained.

45 bp = 190 °C (0.05 mmHg)

45

Elemental analysis C ₂₁ H ₃₈ O ₇ P ₂						
% calc.	C	54.30	H	8.25	P	13.34
% found	C	54.04	H	8.15	P	12.94

50 IR (film):
3400 cm⁻¹: OH
2850: aliphatic C-H
1240: P = O
1060: P-O-C
NMR (CDCl₃):
 δ =

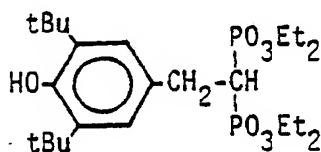
7.0-6.9 (m, 2H): aromatic H
 4.2-4.05 (m, 8H): P-O-CH₂-CH₃
 3.14 (d x t, J = 6 and 18 Hz, 2H): Ph-CH₂
 2.6 (t x t, J = 6 and 24 Hz, 1H): Ph-CH₂-CH
 5 2.2 (s, 3H): CH₃
 1.4 (s, 9H): t-C₄H₉
 1.25 (2 x t, 12H): P-O-CH₂-CH₃

10 Example 9 (Compound 4)

Tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethyldene-1,1-diphosphonate

15

20



A 80 ml ethanol solution of tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethyldene-1,1-diphosphonate (25.3 g, 50 mmol) (compound 33) was added under nitrogen to a suspension of lithium borohydride (3.3 g, 150 mmol) in 250 ml ethanol and the mixture was refluxed for 1 h. The solvent was evaporated and the residue was taken up in diethyl ether. The ether phase was washed with a 10% HCl solution, H₂O until pH 6 and then dried over MgSO₄. Evaporation of the ether solution gave 24 g (47 mmol, 95% yield) of tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethyldene-1,1-diphosphonate.

The reduction of compound 33 can also be carried out by catalytic hydrogenation.

30 A mixture of compound 33 (1 g, 2 mmol) and 20 mg of 10% Palladium on active charcoal (10% Pd/C) in 50 ml acetic acid was hydrogenated at room temperature and 1.5 atm pressure for 16 h. Filtration of the catalyst and evaporation of the solvent gave 1.0 g (2 mmol, 100%) of the title compound.

35 Platinum on active charcoal (10% Pt/C) can also be used with equally good results. A mixture of compound 33 (1 g, 2 mmol) and 20 mg 10% Pt/C in 50 ml CH₃COOH was hydrogenated at room temperature and 1.2 atm for 16 h and gave after work up 1 g of compound 4 (2 mmol, 100%).

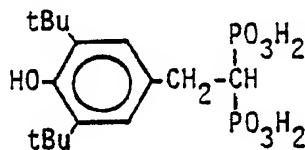
The compound prepared by these reduction procedures has physical and spectroscopic data identical to those of the product described in example 3.

40 Example 10 (Compound 8)

2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethyldene-1,1-diphosphonic acid

45

50



Under anhydrous conditions, trimethylbromosilane (5 ml, 38.6 mmol) was added dropwise to 10 ml of a carbon tetrachloride solution of tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethyldene-1,1-diphosphonate (1.95 g, 3.86 mmol). The mixture was stirred at room temperature for 30 h. The excess of BrSiMe₃ was removed by distillation and the residue was treated with 20 ml H₂O for 2 h. Evaporation of the aqueous solution gave 1.43 g (3.6 mol, 94%) of the diphosphonic acid.

mp = 177-178 °C

IR (KBr):

3600 cm^{-1} : OH
 3000-2500: P-O-H
 1430: t-C₄H₉
 5 1200: P=O

Compound 8 can also be obtained by hydrolysis with hydrochloric acid.

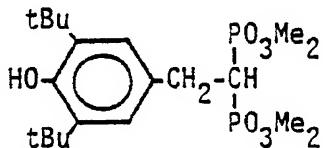
A mixture of compound 4 (2.5 g, 50 mmol) in 10 ml 37% HCl was heated to 115° for 16 h. The evaporation to dryness of HCl provided 1.9g (4.8 mmol, 96%) of 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonic acid.

10

Example 11 (Compound 10)

15 Tetramethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate

20



25

A mixture of 3.5 g (8.9 mmol) 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonic acid and 10 g (94 mmol) trimethylorthoformate was refluxed for one hour. The methyl formate and methanol formed were distilled off. Fresh trimethyl orthoformate (10 g, 94 mmol) was added and the mixture was refluxed for one hour. Removal of excess reagent and short path distillation (200° C, 0.05 mmHg) gave 2.5 g (65%) of tetramethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate.

30 mp = 77-78° C

IR(KBr):

3400 cm^{-1} : O-H
 2850: aliphatic C-H

1430: t-butyl

35 1245: P=O

1185: P-O-Me

1030: P-O-C.

NMR (CDCl₃): δ =

40 7.25 and 7.05 (m, 2H): aromatic H

5.0 (s, 1H): OH

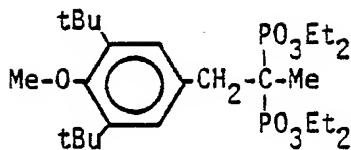
3.7 - 3.65 (two d, J = 11 Hz, 12H): P-O-CH₃3.1 (t x d, J = 6 and 17 Hz, 2H): Ph-CH₂2.6 (t x t, J = 6 and 24 Hz, 1H): Ph-CH₂-CH45 1.35 (s, 18H) : t-C₄H₉

Example 12 (Compound 15)

50

Tetraethyl 1-(3,5-ditertiobutyl-4-methoxyphenyl)propylidene 2,2-diphosphonate

55

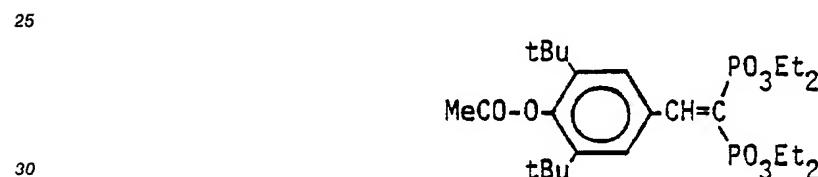


10 Tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethyldene-1,1-diphosphonate (500 mg, 1 mmol) was added to a suspension of 80% NaH (40 mg, 1.3 mmol) in 20 ml dry THF. Methyl iodide (1.3 ml, 6 mmol) was added and the reaction mixture was refluxed for 16 h. After Et₂O/H₂O extraction, the organic phase was dried and evaporated. Column chromatography (SiO₂, 95/5 CHCl₃/MeOH) gave 440 mg (0.84 mmol, 84%) of the title compound.

IR:
 2980 cm⁻¹: aliphatic C-H
 1240: P = O
 1030: P-O-C
 MS: 534 (M⁺), 397 (100%, M-PO₃Et₂)⁺, 233

20 Example 13 (Compound 41)

Tetraethyl 2-(3,5-ditertiobutyl-4-acetoxyphenyl)-ethenylidene-1,1-diphosphonate

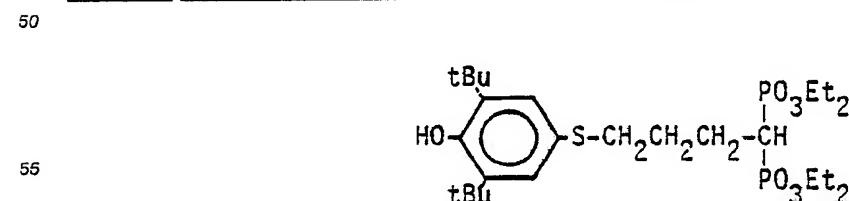


35 A mixture of tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate (3 g, 6 mmol) and a catalytic amount (50 mg) H₂SO₄ in 3 g of acetic anhydride was warmed to 80 °C for 3 h. The reaction mixture was poured on ice and extracted in Et₂O. The organic phase was washed with H₂O and dried over MgSO₄ and evaporated to dryness. The residue was purified by column chromatography (SiO₂, 95/5 CHCl₃/MeOH) to give 2.32 g (4.2 mmol, 71% yield) of the title compound.

IR:
 2840 cm¹: aliphatic C-H
 1760: C = O
 1560: C = C
 1240: P = O
 1030: P-O-C

45 Example 14 (Compound 17)

Tetraethyl 4-(3,5-ditertiobutyl-4-hydroxyphenylthio)-butylidene-1,1-diphosphonate



A mixture of 1.0 g (3.04 mmol) of tetraethyl 3-butenylidene-1,1-diphosphonate prepared by reaction of tetraethyl methylene diphosphonate and allyl bromide, 0.8 g (3.36 mmol) of 3,5-ditertiobutyl-4-hydroxyphenylmercaptan and 0.022 g (0.09 mmol) of dibenzoylperoxide was refluxed in benzene overnight. After evaporation of the solvent, the crude product was column chromatographed and 0.44 g (25% yield) of 5 tetraethyl 4-(3,5-ditertiobutyl-4-hydroxyphenylthio)-butylidene-1,1-diphosphonate was isolated.

IR (film):

3400 cm^{-1} : O-H

2850: aliphatic C-H

1430: t-butyl

10 1240: P=O

1020: P-O-C

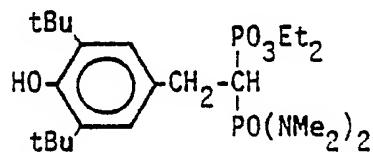
MS: 566 (M^+), 429 ($M-\text{PO}_3\text{Et}_2$)⁺

15 Example 15 (Compound 19)

Diethyl 1-bis(dimethylamino)phosphinyl-2-(3,5-ditertiobutyl-4-hydroxyphenyl)ethylphosphonate

20

25



Diethyl bis(dimethylamino)phosphinyl methylphosphonate was prepared by reacting diethyl methylphosphonate and bis(dimethylamino) phosphorochloridate using lithium diisopropylamide in THF, according to P. Savignac et al, Tetrahedron Letters 26 (37), p. 4435-4438 (1985).

Diethyl bis(dimethylamino)phosphinyl methylphosphonate (1.4 g, 5 mmol) was added at room temperature to a suspension of 80% NaH (0.15 g, 5 mmol) in 20 ml dry tetrahydrofuran. A solution of 3,5-ditertiobutyl-4-hydroxybenzylbromide (1.5 g, 5 mmol) in 20 ml dioxane was added and the mixture was refluxed overnight. After evaporation of the solvents, the residue was partitioned between H_2O and CHCl_3 .

35 The residue of the organic phase was purified by column chromatography (SiO_2 , 95/5 $\text{CHCl}_3/\text{MeOH}$) to give 490 mg (20% yield) of the title compound.

IR (film):

3400 cm^{-1} : OH

2860: aliphatic C-H

40 1440: t-C₄H₉

1240 + 1220: P=O

1030: P-O-C

MS: (m/e): 504 (M^+); 369 (100%, $M^+-\text{PO}(\text{NMe}_2)_2$); 135 ($\text{PO}(\text{NMe}_2)_2$)⁺

NMR (CDCl_3)

45 δ =

7.08 (s, 2H): aromatic H

5.08 (s, 1H): OH

4.1-3.9 (m, 4H): P-O-CH₂CH₃

3.25-3.1 (large m, 2H): Ph-CH₂-CH

50 2.9-2.7 (large m, 1H): Ph-CH₂-CH

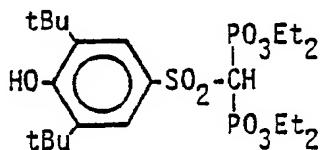
2.5 and 2.55 (two d, $J=9$ Hz, 12H): N-CH₃

1.38 (s, 18H): t-C₄H₉

1.15 (two t, $J=7$ Hz, 6H): P-O-CH₂-CH₃

55

Example 16 (Compound 16)

Tetraethyl 3,5-ditertiobutyl-4-hydroxyphenylsulfonylmethylenediphosphonate

A solution of 800 mg (1.26 mmol) of 49.5% KHSO_5 (Potassium hydrogen persulfate, "oxone") in 0.8 ml H_2O was added to a solution of 400 mg of tetraethyl 3,5-ditertiobutyl-4-hydroxyphenylthio-methylene diphosphonate (compound 5) (0.84 mmol) in 5 ml CH_3OH while stirring in an ice bath. The resulting slurry is stirred overnight and the mixture is concentrated to remove MeOH . The residue is partitioned between H_2O and CH_2Cl_2 . The organic phase is washed with H_2O until neutral pH, concentrated and the residue is purified by column chromatography ($\text{CHCl}_3/\text{MeOH}$). An amount of 200 mg (0.36 mmol, 29%) of tetraethyl 3,5-ditertiobutyl-4-hydroxyphenylsulfonyl-methylenediphosphonate was obtained.

mp = 118-120 °C

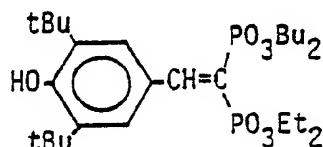
MS: (m/e): 556 (M^+), 492 ($(\text{M}-\text{SO}_2)_2^+$, 100%), 355 ($\text{M}-\text{PO}_3\text{Et}_2$)⁺

20 A mixture of compound 5 (400 mg, 0.76 mmol) and 85% m-chloroperbenzoic acid (0.5 g, 2.5 mmol) in 5 ml CH_2Cl_2 was stirred at room temperature for 16 h. The organic solution was extracted with saturated NaHSO_3 , saturated NaHCO_3 and dried over MgSO_4 . Column chromatography purification ($\text{CHCl}_3/\text{MeOH}$) gave 160 mg of compound 16 (0.28 mmol, 38%).

25

Example 17 (Compound 42)Dibutyl diethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate

30



Dibutyl diethyl methylenediphosphonate was prepared in 43% yield by reacting sodium dibutyl phosphite with diethyl chloromethylphosphonate, bp = 140 °C (0.05 mmHg), (Kugelrohr).

40 Dibutyl diethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate was synthesized by reacting TiCl_4 (4.94 g, 26 mmol), 3,5-ditertiobutyl-4-hydroxybenzaldehyde (3 g, 13 mmol), dibutyl diethyl methylenediphosphonate (4.4 g, 13 mmol) and N-methylmorpholine (5.25 g, 52 mmol) in 20 ml THF at room temperature. Column chromatography (95/5 $\text{CHCl}_3/\text{MeOH}$) afforded 2.6 g (4.6 mmol, 36%) of the title compound.

45 IR (film):

2980 cm^{-1} : aliphatic C-H

1560: C=C

1430: t-C₄H₉

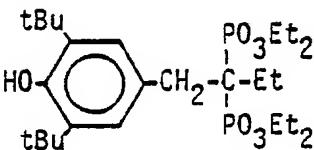
50 1240: P=O

1020-970: P-O-C

MS: (m/e): 560 (M^+), 423 ($\text{M}-\text{PO}_3\text{Et}_2$)⁺, 367 ($\text{M}-\text{PO}_3\text{Bu}_2$)⁺, 311

55

Example 18 (Compound 21)Tetraethyl 1-(3,5-ditertiobutyl-4-hydroxyphenyl)-butylidene-2,2-diphosphonate



Tetraethyl propylidene-1,1-diphosphonate was prepared in 65% yield by reacting tetraethyl methylenediphosphonate with ethyl iodide in presence of NaH in tetrahydrofuran.

10 Tetraethyl propylidene-1,1-diphosphonate (1.5 g, 4.75 mmol) was added to a suspension of 80% NaH (0.143 g, 4.75 mmol) in dry THF (10 ml) and the mixture was stirred until the NaH disappeared. 3,5-ditertiobutyl-4-hydroxybenzylbromide (1.42 g, 4.75 mmol) in 5 ml THF was added and the mixture was refluxed for 4 h. After work up, column chromatography (SiO₂, 95/5 CHCl₃/MeOH) gave 0.9 g (1.7 mmol, 36%) of the title compound. mp = 107-110 °C

15 IR (film):

3400 cm⁻¹: OH

2850: aliphatic C-H

1440: t-butyl

1240: P=O

20 1040: P-O-C

NMR (CDCl₃)

δ =

7.15 (m, 2H): aromatic H

5.1 (s, 1H): OH

25 4.2 - 4.04 (m, 8H): O-CH₂-CH₃

3.2 (two d, J = 12 and 16 Hz, 2H): Ph-CH₂-CP₂

2.1 - 1.9 (m, 2H): -C(P₂)-CH₂-CH₃

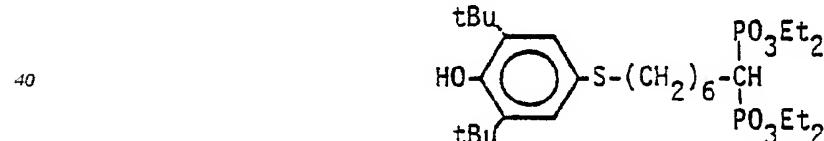
1.45 (s, 18H): tC₄H₉

1.3 - 1.15 (several t, J = 7Hz, 15H): -C(P₂)-CH₂-CH₃ + O-CH₂CH₃

30

Example 19 (Compound 20)

35 Tetraethyl 7-(3,5-ditertiobutyl-4-hydroxyphenylthio)-heptylidene-1,1-diphosphonate



45 Tetraethyl 7-bromoheptylidene-1,1-diphosphonate was prepared by reaction of sodium tetraethyl methylenediphosphonate with 1,6-dibromohexane.

A 20 ml tetrahydrofuran solution containing 4.2 mmol of the sodium salt of 3,5-ditertiobutyl-4-hydroxyphenyl mercaptan was added to 20 ml of a tetrahydrofuran solution containing tetraethyl 7-bromoheptylidene-1,1-diphosphonate (1.89 g, 4.2 mmol). The reaction mixture was stirred at room temperature overnight. After hydrolysis and extraction into Et₂O, the crude compound was purified by column chromatography (SiO₂, 95/5 CHCl₃/MeOH) to yield 1.6 g (2.63 mmol, 62%) of the title compound.

IR (film):

3400 cm⁻¹: OH

2940: aliphatic C-H

55 1430: t-C₄H₉

1250: P=O

1030 + 980: P-O-C

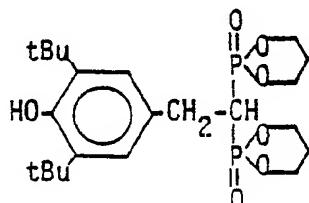
MS: (m/e): 608 (M⁺), 371, 288 (100%), 152

Example 20 (Compound 24)

2-(3,5-ditertiobutyl-4-hydroxyphenyl)ethylidene-1,1-bis(2-oxo-1,3,2-dioxaphosphorinan)

5

10



15

Treatment of tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)ethylidene-1,1-diphosphonate with BrSiMe₃ gave the corresponding tetrakis(trimethylsilyl) diphosphonate. This latter compound was reacted with PCl₅ in CCl₄ according to the reaction conditions described by T. Morita et al, Chemistry Letters p. 435-438 (1980) to afford 2-(3,5-ditertiobutyl-4-hydroxyphenyl)ethylidene-1,1 diphosphonyl tetrachloride.

20

To a solution of Et₃N (7.86g, 78 mmol) in 80 ml dioxane held at 55° were added simultaneously the above described diphosphonyl tetrachloride (9.0g, 19 mmol) in 40ml dioxane and 1,3-propanediol (2.90g, 38 mmol) in 40 ml dioxane. The reaction mixture was refluxed for 3 h after the end of the addition. The precipitate of Et₃N.HCl was removed by filtration and the filtrate was purified by column chromatography (SiO₂, CHCl₃/MeOH 95/5). An amount of 1.35 g (2.9 mmol, 15% yield) of the title compound was obtained.

25

mp = 175-176 °C

IR (KBr) = 3400, 1430, 1260 (P = O), 1040 (P-O-C)

MS (m/e)⁺ = 474 (M⁺), 353 (100%, M-PO₃(C₃H₆)₂)⁺ NMR (CDCl₃)

δ =

7.25 and 7.1 (m, 2H): aromatic H

30

5.1 (s, 1H): OH

4.45, 4.3 and 4.1 (3m, 8H): P-O-(CH₂)-

3.26 (dxt, J = 6 and 17Hz, 2H): Ph-CH₂-CH-

2.80 (txt, J = 7 and 23 Hz, 1H): Ph-CH₂-CH-

2.1 and 1.9 (2m, 4H): P-O-CH₂-CH₂-CH₂-

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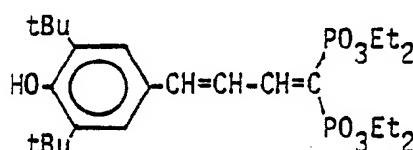
1.4 (s, 18H): t-C₄H₉

Example 21 (Compound 43)

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Tetraethyl 4-(3,5-ditertiobutyl-4-hydroxyphenyl)-1,3-butadienylidene-1,1-diphosphonate

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Titanium tetrachloride (3.14g, 0.017 mol) was dropped, under nitrogen, to 40 ml of anhydrous THF cooled in an ice bath. It was successively added 2.15g (0.008 mol) of 3,5-ditertiobutyl-4-hydroxy-cinnamaldehyde, 2.39g (0.008 mol) of tetraethyl methylenediphosphonate and 3.25 g (0.033 mol) of methylmorpholine. The resulting mixture was kept in the ice bath for a further 1 hour then allowed to return to room temperature overnight. 50 ml of water was added and the resulting mixture was extracted with 3 x 50 ml of ethyl ether. The combined organic phase was washed with 3 x 50 ml of brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography (SiO₂, 95/5 CHCl₃/MeOH) to give 3.6 g (0.0068 mol, 82%) of the crude title compound. The latter was recrystallized from acetone yielding 2.1 g

(0.0040 mol, 48%) of pure product. Melting point was 141-143 °C giving a deep red solution.

IR(KBr):

3360 cm⁻¹: OH

1600, 1550 and 1530: C=C

5 1420 and 1430: tC₄H₉

1200: P=O

1020: P-O-C

MS: m/e: 530 (M⁺), 515 (M-Me), 393 (M-PO₃Et₂)

NMR (CDCl₃)

10 δ =

8.05 - 7.7 (several m, 2H): C=CH-CH=C

7.4 (s, 2H): aromatic H

7.04 (d, J = 15 Hz, 1H): Ph-CH=C

5.6 (s, 1H): OH

15 4.2 (m, 8H): P-O-CH₂CH₃

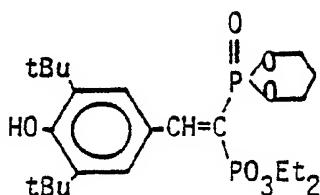
1.45 (s, 18H): t-C₄H₉

1.35 (t, J = 7Hz, 12H): P-O-CH₂CH₃

20 Example 22 (Compound 45)

Diethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl) 1-(2-oxo-1,3,2-dioxaphosphorin-2-yl)ethenyl-1-phosphonate

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Diethyl (2-oxo-1,3,2-dioxaphosphorin-2-yl)methylphosphonate was prepared by the Arbuzov reaction of triethyl phosphite and 2-chloromethyl-2-oxo-1,3,2-dioxaphosphorinan. (IR: 1260 and 1030 cm⁻¹).

The general reaction conditions described in example 6 were employed using diethyl (2-oxo-1,3,2-dioxaphosphorin-2-yl)methylphosphonate as the phosphonate reagent. After work up, purification by column chromatography gave the title compound as an oil in 63% yield.

IR (Film): 3450cm⁻¹, 1570 (C=C), 1420, 1260, 1030 (P-O-C)

40 MS: 488 (M⁺), 367 (M-PO₃Et₂), 351 (M-PO₃(CH₂)₃), 57 (t-Bu)

NMR (CDCl₃)

= 8.2 (d x d, J = 30 and 48 Hz, 1H): Ph-CH=CPO₂Et₂

7.75 (m, 2H): aromatic H

5.65 (m, 1H): OH

45 4.3 - 4.0 (several m, 8H): P-O-CH₂-CH₃ and P-O-CH₂-(CH₂)₂

2.1 - 1.6 (several m, 2H): P-O-CH₂-CH₂-CH₂

1.4 (s, 18H): t-C₄H₉

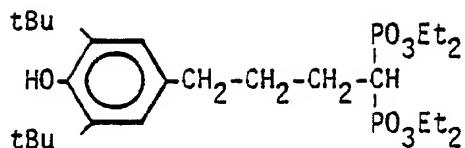
1.4 (t, J = 7Hz): P-O-CH₂-CH₃

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Example 23 (compound 28)

Tetraethyl 4-(3,5-ditertiobutyl-4-hydroxyphenyl)-butyliidene-1,1-diphosphonate

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10 0.5 (0.94 mmol) of tetraethyl 4-(3,5-ditertiobutyl-4-hydroxyphenyl)-1,3-butadienylidene-1,1-diphosphonate (compound 43), 0.23g of 10% palladium on active charcoal in 25ml of glacial acetic acid were submitted to 3 atm. hydrogen gas in a Parr hydrogenation apparatus until no more absorption was observed. The catalyst was filtered. The filtrate was diluted with an equal volume of water and extracted with chloroform. The chloroform phase was washed successively with 10% NaOH, water and dried over MgSO₄. Evaporation of the solvent gave 0.4g of the title compound (98% purity by GC).

15 IR (film) =
3400 cm⁻¹: O-H
2940: aliphatic C-H
1440: t-butyl
1250: P = O
1020: P-O-C

20 NMR (CDCl₃):

δ =
6.96 (s, 2H) : aromatic H
5.03 (s, 1H) : OH
4.24-4.10 (m, 8H): P-O-CH₂-CH₃
25 2.52 (t, J = 7 Hz, 2H): Ph-CH₂-
2.28 (txt, J = 6 and 24Hz, 1H): Ph-CH₂-CH₂-CH₂-CHP₂
2.04-1.78 (2xm, 4H): Ph-CH₂-CH₂-CH₂-CH₂-CHP₂
1.40 (s, 18H): tC₄H₉
1.28 (two overlapping t, J = 7Hz, 12H): P-O-CH₂-CH₃
30 MS: 534 (M⁺)

This compound was chromatographically and spectroscopically identical to the material isolated from the reaction of 3-(3,5-ditertiobutyl-4-hydroxyphenyl)-propyl bromide (mp = 52-54 °C) with the sodium salt of tetraethyl methylenediphosphonate in benzene.

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Table 1: Phenol substituted gem-diphosphonates (Ia)

Cpd	χ^1	χ^2	χ^3	A	B	χ^1	χ^2	χ^3	χ^4	mp or bp (mm Hg), °C	Formula ^a
1	3-Me	5-t-Bu	4-H	CH ₂	H	0Et	0Et	0Et	0Et	190(0.05)	C ₂₁ H ₃₈ O ₇ P ₂
2	3-i-Pr	5-i-Pr	4-H	CH ₂	H	0Et	0Et	0Et	0Et	195(0.05)	C ₂₂ H ₄₀ O ₇ P ₂
3	3-sec-Bu	5-sec-Bu	4-H	CH ₂	H	0Et	0Et	0Et	0Et	200(0.05)	C ₂₄ H ₄₄ O ₇ P ₂
4	3-t-Bu	5-t-Bu	4-H	CH ₂	H	0Et	0Et	0Et	0Et	62-63	C ₂₄ H ₄₄ O ₇ P ₂
5	3-t-Bu	5-t-Bu	4-H	S	H	0Et	0Et	0Et	0Et	78-80	C ₂₃ H ₄₂ O ₇ P ₂ S
6	3-t-Bu	5-t-Bu	4-H	CH ₂	H	0i-Pr	0i-Pr	0i-Pr	0i-Pr	104-105	C ₂₈ H ₅₂ O ₇ P ₂
7	3-t-Bu	5-t-Bu	4-H	CH ₂	H	0n-Bu	0n-Bu	0n-Bu	0n-Bu	b	C ₃₂ H ₆₀ O ₇ P ₂
8	3-t-Bu	5-t-Bu	4-H	CH ₂	H	0H	0H	0H	0H	177-178	c
9	3-t-Bu	5-t-Bu	4-H	S	H	0H	0H	0H	0H	183-185	c
10	3-t-Bu	5-t-Bu	4-H	CH ₂	H	0Me	0Me	0Me	0Me	77-78	C ₂₀ H ₃₆ O ₇ P ₂
11	3-OMe	5-OMe	4-H	CH ₂	H	0Et	0Et	0Et	0Et	b	d
12	3-OMe	5-OMe	4-Me	CH ₂	H	0Et	0Et	0Et	0Et	205(0.05)	C ₁₉ H ₃₄ O ₉ P ₂
13	6-Cl	3,4-OCH ₂ ⁻		CH ₂	H	0Et	0Et	0Et	0Et	200(0.05)	C ₁₇ H ₂₇ C ₁₀ O ₈ P ₂

^a = analyzed for C, H, P; results within 0.4% of theoretical values^b = purified by column chromatography^c = characterized by NaOH titration^d = characterized by IR and MS spectroscopies

55 50 45 40 35 30 25 20 15 10 5 0

Table 1: Phenol substituted gem-diphosphonates (1a) (cont.)



cpd	χ^1	χ^2	χ^3	χ^4	A	B	Z^1	Z^2	Z^3	Z^4	mp or bp (mm Hg), °C	Formula ^a
14	3-t-Bu	5-t-Bu	H	$(\text{CH}_2)_2$	H	0Et	0Et	0Et	0Et	0Et	b	$\text{C}_{25}\text{H}_{46}\text{O}_7\text{P}_2$
15	3-t-Bu	5-t-Bu	Me	CH_2	Me	0Et	0Et	0Et	0Et	0Et	b	$\text{C}_{26}\text{H}_{48}\text{O}_7\text{P}_2$
16	3-t-Bu	5-t-Bu	4-H	SO_2	H	0Et	0Et	0Et	0Et	0Et	118-120	$\text{C}_{23}\text{H}_{42}\text{O}_9\text{P}_2\text{S}$
17	3-t-Bu	5-t-Bu	4-H	$\text{S}(\text{CH}_2)_3$	H	0Et	0Et	0Et	0Et	0Et	b	d
18	3-t-Bu	5-t-Bu	4-H	CH_2	H	0Et	0Et	0Et	0Et	0Et	b	$\text{C}_{28}\text{H}_{52}\text{O}_7\text{P}_2$
19	3-t-Bu	5-t-Bu	4-H	CH_2	H	0Et	0Et	0Et	0Et	0Et	b	$\text{C}_{24}\text{H}_{46}\text{N}_2\text{O}_5\text{P}_2$
20	3-t-Bu	5-t-Bu	4-H	$\text{S}(\text{CH}_2)_6$	H	0Et	0Et	0Et	0Et	0Et	b	$\text{C}_{29}\text{H}_{54}\text{O}_7\text{P}_2\text{S}$
21	3-t-Bu	5-t-Bu	4-H	CH_2	Et	0Et	0Et	0Et	0Et	0Et	107-110	$\text{C}_{26}\text{H}_{48}\text{O}_7\text{P}_2$
22	3-t-Bu	5-t-Bu	4-H	S	H	0i-Pr	0i-Pr	0i-Pr	0i-Pr	0i-Pr	106-108	$\text{C}_{17}\text{H}_{50}\text{O}_7\text{P}_2$
23	3-t-Bu	5-t-Bu	4-H	CH_2	H	0n-Pr	0n-Pr	0n-Pr	0n-Pr	0n-Pr	73-74	$\text{C}_{28}\text{H}_{52}\text{O}_7\text{P}_2$
24	3-t-Bu	5-t-Bu	4-H	CH_2	H	0-(CH_2) ₃ -O	173-174	$\text{C}_{22}\text{H}_{36}\text{O}_7\text{P}_2$				
25	3-t-Bu	5-t-Bu	4-H	CH_2	H	0Et	0Et	0i-Pr	0i-Pr	0i-Pr	59-60	$\text{C}_{26}\text{H}_{48}\text{O}_7\text{P}_2$
26	3-sec-Bu	5-sec-Bu	4-H	CH_2	H	0i-Pr	0i-Pr	0i-Pr	0i-Pr	0i-Pr	b	$\text{C}_{28}\text{H}_{52}\text{O}_7\text{P}_2$
27	3-t-Bu	5-t-Bu	4-H	CH_2	H	$\text{OCCH}_2-\text{CMe}_2-\text{CH}_2$	$\text{OCCH}_2-\text{CMe}_2-\text{CH}_2$	$\text{OCCH}_2-\text{CMe}_2-\text{CH}_2$	$\text{OCCH}_2-\text{CMe}_2-\text{CH}_2$	$\text{OCCH}_2-\text{CMe}_2-\text{CH}_2$	66-67	$\text{C}_{26}\text{H}_{44}\text{O}_7\text{P}_2$
28	3-t-Bu	5-t-Bu	4-H	$(\text{CH}_2)_3$	H	0Et	0Et	0Et	0Et	0Et	b	d
29	3-t-Bu	5-t-Bu	4-H	$\text{CH}=\text{CH-CH}_2$	H	0Et	0Et	0Et	0Et	0Et	b	d

^a = analyzed for C, H, P; results within 0.4% of theoretical values^b = purified by column chromatography^c = characterized by NaOH titration^d = characterized by IR and MS spectroscopies

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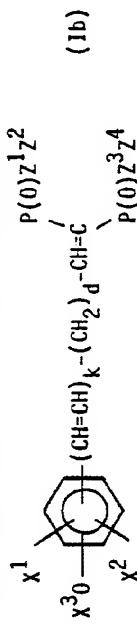
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Table 2: Phenol substituted gem-diphosphonates (1b)



Compound	X^1	X^2	X^3	X^4	k	d	Z^1	Z^2	Z^3	Z^4	mp or bp (mm Hg), °C	Formula ^a
30	3-Me	5-t-Bu	4-H		0	0	0Et	0Et	0Et	0Et	b	$\text{C}_{21}\text{H}_{36}\text{O}_7\text{P}_2$
31	3-i-Pr	5-i-Pr	4-H		0	0	0Et	0Et	0Et	0Et	97-100	$\text{C}_{22}\text{H}_{38}\text{O}_7\text{P}_2$
32	3-sec-Bu	5-sec-Bu	4-H		0	0	0Et	0Et	0Et	0Et	102-105	$\text{C}_{24}\text{H}_{42}\text{O}_7\text{P}_2$
33	3-t-Bu	5-t-Bu	4-H		0	0	0Et	0Et	0Et	0Et	120-121	$\text{C}_{24}\text{H}_{42}\text{O}_7\text{P}_2$
34	3-t-Bu	5-t-Bu	4-H		0	0	0i-Pr	0i-Pr	0i-Pr	0i-Pr	131-132	$\text{C}_{28}\text{H}_{50}\text{O}_7\text{P}_2$
35	3-t-Bu	5-t-Bu	4-H		0	0	0n-Bu	0n-Bu	0n-Bu	0n-Bu	59-61	$\text{C}_{32}\text{H}_{58}\text{O}_7\text{P}_2$
36	3-t-Bu	5-t-Bu	4-H		0	0	0H	0H	0H	0H	135-137	c
37	3-OMe	5-OMe	4-H		0	0	0Et	0Et	0Et	0Et	53-55	$\text{C}_{18}\text{H}_{30}\text{O}_9\text{P}_2$
38	H	$3,4\text{-OCH}_2^-$	0	0	0Et	0Et	0Et	0Et	0Et	0Et	b	$\text{C}_{17}\text{H}_{26}\text{O}_8\text{P}_2$
39	H	$3,4\text{-O}(\text{CH}_2)_2^-$	0	0	0Et	0Et	0Et	0Et	0Et	0Et	b	$\text{C}_{18}\text{H}_{28}\text{O}_8\text{P}_2$
40	3-t-Bu	5-t-Bu	4-Me		0	0	0Et	0Et	0Et	0Et	b	$\text{C}_{24}\text{H}_{44}\text{O}_7\text{P}_2$
41	3-t-Bu	5-t-Bu	4-MeCO		0	0	0Et	0Et	0Et	0Et	b	$\text{C}_{26}\text{H}_{44}\text{O}_8\text{P}_2$
42	3-t-Bu	5-t-Bu	4-H		0	0	0Et	0Et	0Bu	0Bu	b	$\text{C}_{28}\text{H}_{50}\text{O}_7\text{P}_2$
43	3-t-Bu	5-t-Bu	4-H	1	0	0Et	0Et	0Et	0Et	141-143	$\text{C}_{26}\text{H}_{44}\text{O}_7\text{P}_2$	
44	3-t-Bu	5-t-Bu	4-H	2	0Et	0Et	0Et	0Et	0Et	0Et	b	d
45	3-t-Bu	5-t-Bu	4-H	0	0	$0(\text{CH}_2)_3\text{O}$	0Et	0Et	0Et	0Et	b	$\text{C}_{23}\text{H}_{48}\text{O}_7\text{P}_2$

^a = analyzed for C, H, P; results within 0.4% of theoretical values

b = purified by column chromatography

c = characterized by NaOH titration

d = characterized by IR and MS spectroscopies

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Table 2: Phenol substituted gem-diphosphonates (Ib) (cont.)

Compound	χ^1	χ^2	χ^3	k	d	χ^1	χ^2	χ^3	χ^4	mp or bp (mm Hg), °C	Formula ^a
46	3-t-Bu	5-t-Bu	2-H	0	0	0Et	0Et	0Et	0Et	143-145	$C_{24}H_{42}O_7P_2$
47	3-t-Bu	5-t-Bu	4-H	0	0	0Me	0Me	0Me	0Me	95-96	$C_{20}H_{34}O_7P_2$
48	3-t-Bu	5-t-Bu	4-H	0	0	0n-Pr	0n-Pr	0n-Pr	0n-Pr	85-87	$C_{28}H_{50}O_7P_2$
49	3-t-Bu	5-t-Bu	4-H	0	0	0Et	0Et	0i-Pr	0i-Pr	106-107	$C_{26}H_{46}O_7P_2$
50	3-sec-Bu	5-sec-Bu	4-H	0	0	0i-Pr	0i-Pr	0i-Pr	0i-Pr	b	$C_{28}H_{50}O_7P_2$
51	3-t-Bu	5-t-Bu	4-H	0	0	0(CH ₂) ₃ 0	207-213	$C_{22}H_{34}O_7P_2$			

^a = analyzed for C, H, P; results within 0.4% of theoretical values

b = purified by column chromatography

c = characterized by NaOH titration

d = characterized by IR and MS spectroscopies

PHARMACOLOGICAL ACTIVITY OF GEM-DIPHOSPHONATES OF FORMULA (I)

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During routine screening the gem-diphosphonate derivatives were discovered to display a spectrum of pharmacological activities, the most marked being hypolipidemia (hypcholesterolemia and/or hypotriglyceridemia). Some of the diphosphonic acid derivatives demonstrated anti-inflammatory activity and some diphosphonate esters were hypotensive. Diuretic and positive inotropic activity were also observed.

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In addition it might be expected that the gem-diphosphonates possess antioxidant and radical scavenging activities associated with the dialkyl hydroxyphenyl moieties present in their structures. Free radical scavengers are known to be efficacious in preventing the pathological changes in a number of diseases induced by oxidative stress. The gem-diphosphonates are thus potentially useful for the treatment of diseases such as:

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- tissue ischemia such as heart and brain ischemia,
- muscular dystrophy,
- chronic obstructive pulmonary disease,
- viral infections,
- senile caractogenesis and

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- vitamin E deficiencies.

A) Hypolipidemic activity

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With the goal of finding new drugs which might be hypolipidemic, the new diphosphonates described in this patent application were administered orally to mice. This rodent species has plasma lipid levels relatively close to man (generally greater than 150mg/dl). For example, in mice receiving a normal diet the plasma cholesterol and triglyceride levels are in the range of 100mg/dl, whereas for rat the comparative values are close to 50mg/dl. Other scientists have recently investigated the use of mice and found this species to be a relevant model for testing new agents in comparison to drugs known to be efficacious in human hyperlipidemia (Effects to Fenofibrate, Gemfibrozil and Nicotinic Acid on Plasma Lipoprotein Levels in Normal and Hyperlipidemic Mice, a Proposed Model for Drug Screening. Olivier, P. et al. Atherosclerosis 70, p.107-114, 1988).

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1) Methods

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In every screening experiment, 30 mice of the OF1 strain weighting 25 to 35 g were divided into 5 groups of 6 animals each. Four groups received the compounds to be tested, or the reference drugs, the fifth group served as control. Compounds were dissolved in diethyl ether, the solution was added to the pelleted food and the ether was evaporated.

All compounds were tested at the final concentration of 0.1% in animal chow, equivalent to a daily intake of about 180 mg/kg. This diet was fed for 10 days, then after an overnight fasting the animals were sacrificed by decapitation under ether anesthesia. Blood samples were collected in EDTA containing tubes.

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Plasma cholesterol and plasma triglycerides were measured by enzymatic methods (Ames kit No. 6376 and No. 6630). The mean cholesterol or triglyceride value of each group receiving tested compounds or reference drugs was expressed as percent of the mean value observed for the contemporary control.

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2) Results

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Table 3 showed that a number of diphosphonate derivatives (Compounds 3, 4, 5, 6, 7, 18, 21, 22, 23, 24, 33, 34, 37, 47 and 48) were markedly hypcholesterolemic, Compounds 33 and 34 being the most potent (-40% and -41%). Clofibrate, gemfibrozil and fenofibrate, drugs used clinically for the treatment of hyperlipidemia, were found to be less hypcholesterolemic than many of the diphosphonates tested. Fenofibrate was the most potent (-15%) of the references drugs tested. Similar hypcholesterolemic activity was measured in mice receiving the fibrate derivatives as published in the reference cited above (Olivier, P. et al.).

A significant hypotriglyceridemia was observed with Compounds 3, 5, 6, 7, 21, 22, 23, 24, 30, 31, 33, 37, 47 and 48. It should be noted that Compounds 3, 19, 24, 30, 37 and 47 decreased plasma triglycerides by more than 44%, values not reached by the reference drugs tested similarly. Gemfibrozil was the most potent hypotriglyceridemic reference drug (-35%), which is in accordance with values published in the literature.

The exact mechanism by which these diphosphonates lower plasma lipids in various *in vivo* models is not known. However, investigations using *in vitro* preparations have demonstrated that these compounds inhibit and interfere with some key enzymes involved in cholesterol synthesis and metabolism, specifically acyl-CoA: cholesterol acyltransferase (ACAT), lipases, etc., and thus indicate the possible sites of action.

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B) Anti-inflammatory activity

15 1) Methods

The effect of four selected diphosphonates was investigated on the inflammatory response to kappa carrageenan in the rat paw oedema model. Eight male rats were employed per group. Oedema was induced in the right hind paw of each animal by a single injection into the plantar aponeurosis of 0.1 ml of a 1% w/v of kappa carrageenan solution dissolved in 0.9% NaCl. The test compounds (100 mg/kg) and reference drug (indomethacin 30 mg/kg) were administered by gavage 1 hour prior to induction of oedema by carrageenan injection.

The volume of the right paw was measured for each animal at 0, 1, 2.5 and 4 hours after carrageenan injection (only 4 hour values are reported).

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2) Results

Table 4 showed that indomethacin prevented completely the increase in paw volume as expected. Compounds 8 and 36 showed significant inhibitory activities whereas their ethyl ester counterparts demonstrated only minimal activity.

These results indicate that the diphosphonic acids such as Compound 8 are anti-inflammatory in this animal model.

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C) Oral hypotensive activity in hypertensive rats

The spontaneously hypertensive rat (SHR) is a well established animal model of human arterial hypertension. The gem-diphosphonates of formula (I) were found to induce a marked hypotension when administered to SHRs.

In screening experiments various gem-diphosphonates were dissolved in Tween-80 and administered orally to SH rats. Blood pressure was monitored hourly using a tailcuff method. Hypotension measured two hours post dose are given in Table 5.

Compounds 4, 6, 7 and 18 decreased blood pressure by 30 to 50% and are as potent as the reference drugs tested similarly and which are used for the treatment of angina pectoris and hypertension.

The gem-diphosphonates of formula (I) are thus potentially useful in the treatment of cardiovascular diseases via a smooth muscle relaxant activity. The primary indications of these compounds would be the treatment of angina pectoris, congestive heart failure and hypertension.

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TABLE 3

5 HYPOLIPIDEMIC ACTIVITY OF DIPHOSPHONATES OF FORMULA (I)
 AND REFERENCE DRUGS

10	Compounds (I)	Cholesterol (% control)	Triglycerides (% control)
1		- 2	- 28
2		+ 6	- 17
20	4	- 12	- 1
6		- 37	- 34
7		- 23	- 15
25	8	- 2	+ 19
10		- 5	- 19
19		- 6	- 44
30	3	- 19	- 46
5		- 22	- 24
33		- 40	- 21
30		+ 2	- 45
35	31	+ 4	- 11
35		0	+ 7
36		- 9	- 5
40	38	- 5	- 6
13		- 5	+ 38
18		- 31	+ 60
45	20	+ 5	+ 13
21		- 16	- 28
22		- 21	- 37
23		- 15	- 33
50	24	- 20	- 71

TABLE 3 (cont.)

5 HYPOLIPIDEMIC ACTIVITY OF DIPHOSPHONATES OF FORMULA (I)
AND REFERENCE DRUGS

10	Compounds (I)	Cholesterol (% control)	Triglycerides (% control)
15			
	32	+ 8	+ 9
	34	- 41	+ 11
20	37	- 16	- 70
	39	+ 4	+ 17
	41	- 3	+ 6
25	42	+ 12	+ 1
	43	- 5	- 14
	46	+ 1	- 12
	47	- 31	- 45
30	48	- 21	- 36
35	Reference Drugs		
40	Clofibrate	+ 4	- 5
	Gemfibrozil	- 7	- 35
	Fenofibrate	- 15	- 2

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TABLE 4

ANTI-INFLAMMATORY ACTIVITY OF DIPHOSPHONATES OF FORMULA (I) AND INDOMETHACIN	
Inhibition of rat right hind paw volume increase (4 hours post oedema induction)	
Compounds (I)	% Change from control
Compound 4	+ 1.5
Compound 8	- 54.2
Compound 33	- 5.8
Compound 36	- 25.0
Reference Drug	
Indomethacin	- 92.3

TABLE 5

EFFECT OF GEM-DIPHOSPHONATES OF FORMULA (I) ON BLOOD PRESSURE IN HYPERTENSIVE RATS (2 hours post dose)	
Compounds (I)	Percent decrease in blood pressure
4	- 34
6	- 64
7	- 30
18	- 41
3	- 20
Reference Drugs	
Diltiazem	- 38
Nifedipine	- 47

50 MODES OF ADMINISTRATION

The gem-diphosphonates of formula (I) can thus be used for the treatment of hyperlipidemia and/or hypertension and can be administered preferably in the form of capsules, tablets and granules. For this purpose the active principle should be mixed with a pharmaceutical carrier.

55 As used herein, the term "pharmaceutical carrier" denotes a solid or liquid filler diluent or encapsulating substance. Some examples of the substances which can serve as pharmaceutical carriers are sugars, starches, cellulose and its derivatives, powdered tragacanth, malt, gelatin, talc, stearic acid, magnesium stearate, calcium sulfate, vegetable oils, polyols and polyethylene glycol, agar, alginic acid, pyrogen-free

water, isotonic saline and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents and preservatives, can also be present.

The pharmaceutical carrier employed in conjunction with the phosphonates is used at a concentration sufficient to provide a practical size to dosage relationship. Preferably the pharmaceutical carrier comprises from about 0.1% to 99% by weight of the total composition. Capsules and tablets are prepared by conventional methods using gem-diphosphonates in their liquid or crystalline form as described in the following examples:

10

Example of a Capsule Formulation	
Ingredients	mg/Capsule
Compound 7	300
Gelatin	100
Polyethylene glycol 1000	600
Potassium sorbate	0.5

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Example of a Tablet Formulation	
Ingredients	mg/Tablet
Compound 33	500
Hydroxypropylmethyl cellulose	500
Magnesium stearate	3

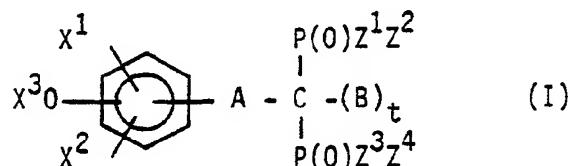
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For the treatment of specific disease states, composition containing a pharmaceutically acceptable gem-diphosphonate can be administered as a solution, suspension, emulsion or by intradermal, intramuscular, intravenous or intraperitoneal injection. Rectal administration of gem-diphosphonates can be performed by incorporating the active principle into conventional jelly bases to produce suppositories.

35 Claims

1. Phenol substituted gem-diphosphonate derivatives of formula (I):

40



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where:

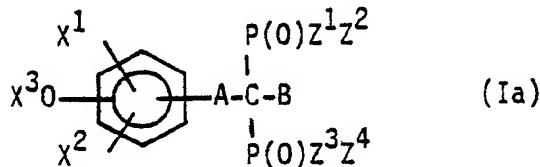
- Z¹, Z², Z³ and Z⁴ identical or different are
- OR where R is H, a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms,
- OM where M is an alkaline or alkaline earth metal ion or an ammonium group NR₄ where R has the same meaning as defined above,
- NR₂ where R has the same meaning as defined above,
- Z¹, Z² and Z³, Z⁴ may form an alkylidenedioxy ring comprising 2 to 8 carbon atoms.
- X¹, X² identical or different, are H, a halogen atom, a straight, branched or cyclic alkyl or alkoxy group from 1 to 8 carbon atoms,
- X³ is H, an alkyl group R¹ from 1 to 4 carbon atoms, an acyl group C(O)R¹, a carbamyl group C(O)NHR¹ where R¹ is described as above; X³O and one of the two other substituents X¹ or X² may form an alkylidenedioxy ring comprising from 1 to 4 carbon atoms,

- A is $-\text{CH}=\text{CH}-\text{CH}_2-$, $-(\text{CH}_2)_n-$, $-\text{O}(\text{CH}_2)_n-$, $-\text{S}-$, $-\text{SO}_2-$, $-\text{S}(\text{CH}_2)_n-$, $-\text{SO}_2(\text{CH}_2)_n-$, where n is an integer from 1 to 7, $-(\text{CH}=\text{CH})_k-(\text{CH}_2)_d-\text{CH}=$ where k is zero or 1 and d is an integer from zero to 4,

- B is H, an alkyl group from 1 to 4 carbon atoms,

- t is zero or 1, with the proviso that t is zero only when A is $(\text{CH}=\text{CH})_k-(\text{CH}_2)_d-\text{CH}=$ where k and d are as described above.

5 2. Phenol substituted alkylidene diphosphonates of formula (Ia) according to claim 1

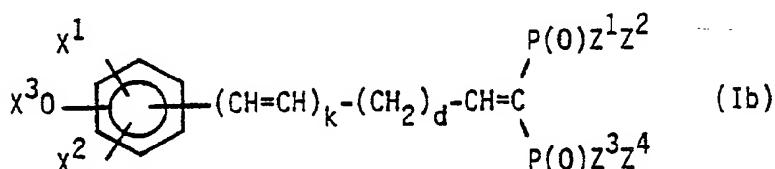


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where X^1 , X^2 , X^3 , A, B, Z^1 , Z^2 , Z^3 , Z^4 are described as above.

3. Phenol substituted alkenylidene diphosphonates of formula (Ib) according to claim 1

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25

where X^1 , X^2 , X^3 , k, d, Z^1 , Z^2 , Z^3 , Z^4 are described as above.

4. Phenol substituted alkylidenediphosphonates of formula (Ia) according to claim 2, selected from the group comprising

30 tetraethyl 2-(3,5-di-secondarybutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate, tetraisopropyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate, tetrabutyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate, tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate, tetraethyl 3,5-ditertiobutyl-4-hydroxyphenylthio-methylene diphosphonate,

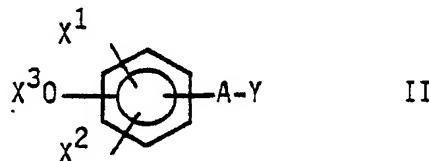
35 2-(3,5-ditertiobutyl-4-hydroxyphenyl)ethylidene-1,1-bis(2-oxo-1,3,2-dioxaphosphorinan) and 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonic acid.

5. Phenol substituted alkenylidenediphosphonates of formula (Ib) according to claim 3, selected from the group comprising

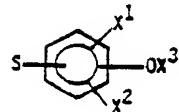
40 tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate, tetraethyl 2-(3-tertiobutyl-4-hydroxy-5-methylphenyl)ethenylidene-1,1-diphosphonate, tetraisopropyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate, tetramethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate and 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonic acid.

45 6. A process for preparing compounds of formula (Ia) according to claim 2, which consists in reacting a compound of formula II

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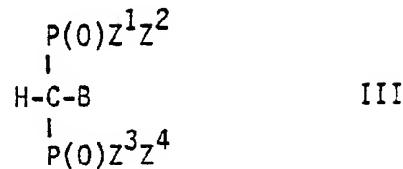


55 where Y = Cl, Br or



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with a diphosphonate compound of formula III



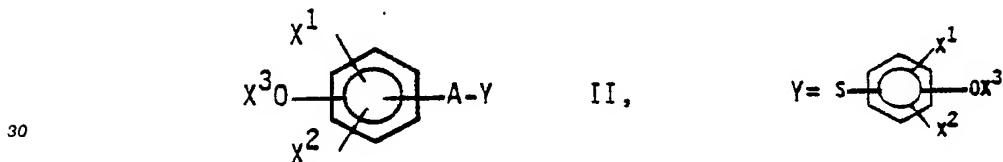
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in presence of a base.

7. A process according to claim 6, where the anion of the diphosphonate compound of formula III, formed in situ by reacting III with a base such as sodium hydride, is reacted with the halide of formula II (II, $\text{Y} = \text{Cl}$ or Br) in an aprotic solvent which is a hydrocarbon such as toluene, benzene or an ether such as tetrahydrofuran, dioxane, dimethoxyethane or a mixture of two of the above solvents at a temperature between 65°C and 110°C .

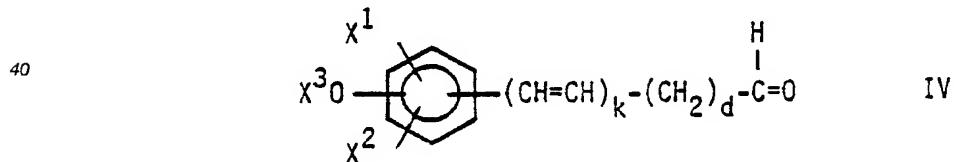
8. A process according to claim 6 when A is S, where the anion of the diphosphonate compound of formula III, formed in situ by reacting III with a base such as n-butyl lithium, is reacted with a disulfide of formula II

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in a solvent such as tetrahydrofuran or benzene at a temperature between -78°C and 40°C .

35 9. A process for preparing compounds of formula (Ib) according to claim 3, which consists in reacting an aldehyde of formula IV



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with a diphosphonate of formula V



55 55 in presence of titanium tetrachloride and a tertiary amine such as pyridine or methyl morpholine in an ether solvent, preferably tetrahydrofuran, dioxane or dimethoxyethane or a mixture of two of the above solvents at temperature between 0°C and 30°C .

10. A process for preparing (la) where $A = (CH=CH)_k-(CH_2)_d-CH_2$ according to claim 2, where the vinylidene-diphosphonate double bond of compounds (lb) are selectively reduced by using a complex hydride such as sodium borohydride or lithium borohydride in ethanol or methanol at a temperature between -15 and 25 °C.

5 11. Process for preparing (la) where $A = (CH_2-CH_2)_k-(CH_2)_d-CH_2$ according to claim 2, where the double bonds of compounds (lb) are completely reduced by using an excess of a complex hydride such as sodium borohydride or lithium borohydride in ethanol or methanol at a temperature between 30 ° and 80 °C.

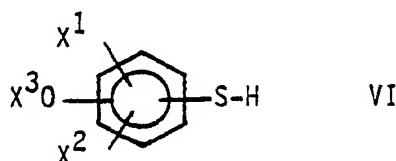
10 12. A process for preparing (la) where $A = (CH_2-CH_2)_k-(CH_2)_d-CH_2$ according to claim 2, where the double bonds of compounds (lb) are completely reduced by catalytic hydrogenation using hydrogen gas as reagent and palladium or platinum adsorbed on active charcoal as catalyst, in polar solvent such as methanol, ethanol, dimethoxyethane, dioxane, tetrahydrofuran or acetic acid at room temperature and at a pressure between 1 atm and 4 atm.

15 13. A process for preparing diphosphonic acid compounds (I) according to claim 1 where $Z^1 = Z^2 = Z^3 = Z^4 = OH$ by hydrolysis of a diphosphonate ester of formula I where $Z^1 = Z^2 = Z^3 = Z^4 = OEt$ with concentrated hydrochloric acid at reflux temperature or with bromotrimethylsilane followed by treatment of water.

14. A process for preparing tetramethyl diphosphonate compounds of formula I according to claim 1, where $Z^1 = Z^2 = Z^3 = Z^4 = OMe$ by reacting the diphosphonic acid as described in claim 13 with trimethyl orthoformate at reflux temperature.

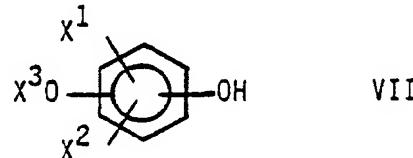
20 15. A process for preparing cyclic esters of diphosphonates of formula (I) according to claim 1, where each of the two substituent pairs Z^1, Z^2 and Z^3, Z^4 forms an alkylidenedioxy ring comprising from 2 to 8 carbon atoms, which consists in reacting the diphosphonyl tetrachloride, prepared by reacting the tetraethyl ester of diphosphonate (I), where $Z^1 = Z^2 = Z^3 = Z^4 = OEt$ sequentially with trimethylbromosilane then with phosphorus pentachloride, with a diol in presence of a tertiary amine in a polar ether solvent such as dioxane at temperature between 20 °C and 100 °C.

25 16. A process for preparing compounds (la) according to claim 2, where $A = -S-(CH_2)_n-$ or $-O-(CH_2)_n-$ which consists in reacting respectively a thiophenol of formula VI,



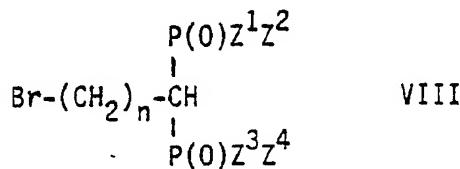
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or a hydroquinone of formula VII



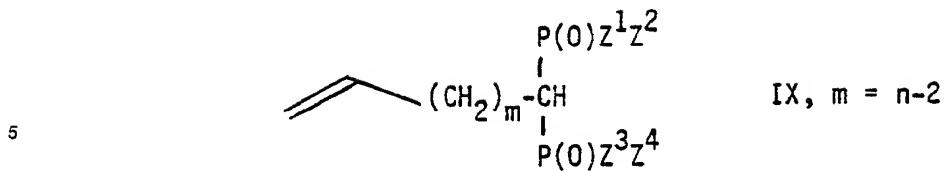
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with a bromoalkylidenediphosphonate of formula VIII



55 in a presence of a base.

17. A process for preparing compounds (la) according to claim 2 where $A = -S(CH_2)_n-$ and $n \geq 3$ which involves reacting the thiophenol of formula VI and an alkenylidenediphosphonate of formula IX



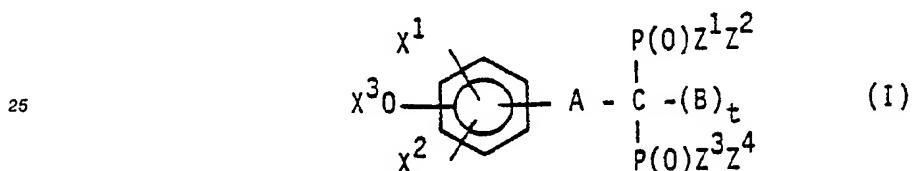
in presence of a radical initiating agent such as dibenzoylperoxide.

10 18. A process for preparing compounds of formula (Ia) according to claim 2 where A is $-\text{SO}_2(\text{CH}_2)_n-$ which consists in oxidizing the compounds (Ia) where A = $-\text{S}-(\text{CH}_2)_n-$ by using m-chloroperbenzoic acid or potassium hydrogen persulfate.

15 19. A pharmaceutical composition comprising a therapeutically effective amount of at least one diphosphonate compound of formula (I) according to claim 1 in combination with a pharmaceutically acceptable carrier.

Claims for the following Contracting States: ES, GR

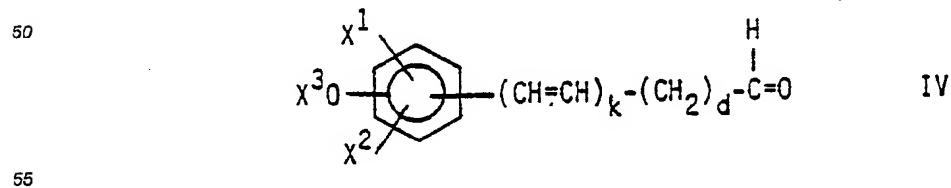
20 1. A process for preparing the phenol substituted gem-diphosphonate derivatives of formula (I):



30 where:

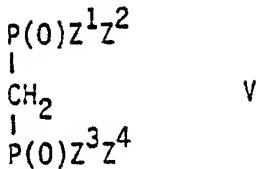
- Z¹, Z², Z³ and Z⁴ identical or different are
- OR where R is H, a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms,
- OM where M is an alkaline or alkaline earth metal ion or an ammonium group NR₄ where R has the same meaning as defined above,
- NR₂ where R has the same meaning as defined above,
- Z¹, Z² and Z³, Z⁴ may form an alkylidenedioxy ring comprising 2 to 8 carbon atoms.
- X¹, X² identical or different, are H, a halogen atom, a straight, branched or cyclic alkyl or alkoxy group from 1 to 8 carbon atoms,
- X³ is H, an alkyl group R¹ from 1 to 4 carbon atoms, an acyl group C(O)R¹, a carbamyl group C(O)NHR¹ where R¹ is described as above; X³O and one of the two other substituents X¹ or X² may form an alkylidenedioxy ring comprising from 1 to 4 carbon atoms,
- A is $-\text{CH}=\text{CH}-\text{CH}_2-$, $-(\text{CH}_2)_n-$, $-\text{O}(\text{CH}_2)_n-$, $-\text{S}-$, $-\text{SO}_2-$, $-\text{S}(\text{CH}_2)_n-$, $-\text{SO}_2(\text{CH}_2)_n-$, where n is an integer from 1 to 7, $-(\text{CH}=\text{CH})_k-(\text{CH}_2)_d-\text{CH}=$ where k is zero or 1 and d is an integer from zero to 4,
- B is H, an alkyl group from 1 to 4 carbon atoms,
- t is zero or 1, with the proviso that t is zero only when A is $(\text{CH}=\text{CH})_k-(\text{CH}_2)_d-\text{CH}=$ where k and d are as described above,

45 which consists in reacting an aldehyde of formula IV



55 with a diphosphonate of formula V

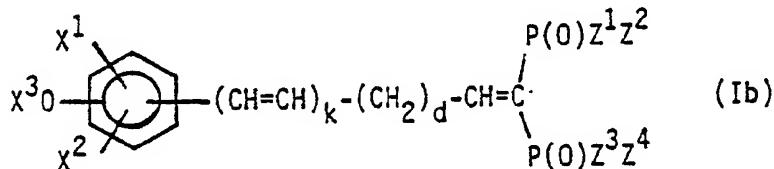
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in presence of titanium tetrachloride and a tertiary amine in an aprotic solvent at temperature between 0 °C and 30 °C to yield the phenol substituted alkenylidene diphosphonate of formula (Ib),

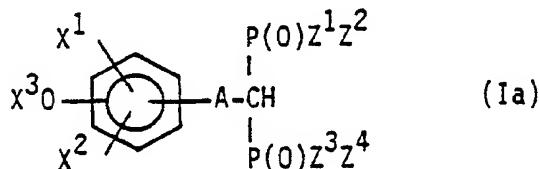
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then reacting compound (Ib) with a reducing agent to yield the phenol substituted alkylidene diphosphonate of formula (Ia),

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where A = (CH=CH)_k-(CH₂)_d-CH₂ or (CH₂-CH₂)_k-(CH₂)_d-CH₂.

2. A process for the preparation of (Ib) according to claim 1, where the catalyst is titanium tetrachloride, the tertiary amine is pyridine or methyl morpholine and the aprotic solvent is tetrahydrofuran, dioxane, dimethoxyethane, carbon tetrachloride or a mixture of any of these solvents.

35

3. A process for preparing (Ia) where A = (CH=CH)_k-(CH₂)_d-CH₂ according to claim 1, where the vinylidene-diphosphonate double bond of compounds (Ib) are selectively reduced by using a complex hydride such as sodium borohydride or lithium borohydride in ethanol or methanol at a temperature between -15 ° and 25 °C.

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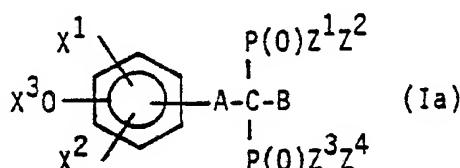
4. A process for preparing (Ia) where A = (CH₂-CH₂)_k-(CH₂)_d-CH₂ according to claim 1, where the double bonds of compounds (Ib) are completely reduced by using an excess of a complex hydride such as sodium borohydride or lithium borohydride in ethanol or methanol at a temperature between 30 ° and 80 °C.

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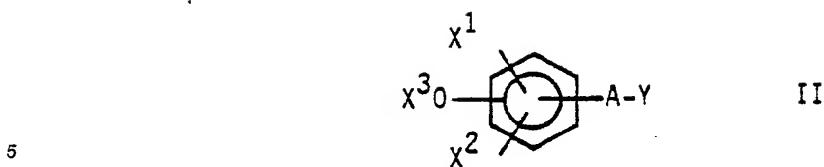
5. A process for preparing (Ia) where A = (CH₂-CH₂)_k-(CH₂)_d-CH₂ according to claim 1 where the double bonds of compounds (Ib) are completely reduced by catalytic hydrogenation using hydrogen gas as reagent and palladium or platinum adsorbed on active charcoal as catalyst, in a polar solvent such as methanol, ethanol, dimethoxyethane, dioxane, tetrahydrofuran or acetic acid at room temperature and at a pressure between 1 atm and 4 atm.

6. A process for preparing compounds of formula (Ia)

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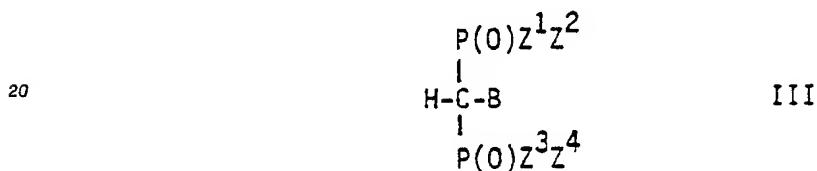
where X¹, X², X³, A, B, Z¹, Z², Z³, Z⁴ are as described in claim 1, which consists in reacting a compound of formula II



where Y = Cl, Br or



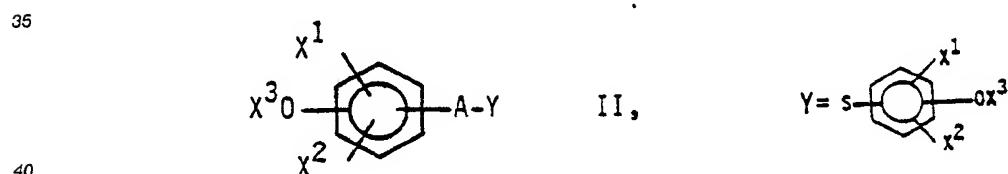
15 with a diphosphonate compound of formula III



25 in presence of a base.

7. A process according to claim 6, where the anion of the diphosphonate compound of formula III, formed in situ by reacting III with a base such as sodium hydride, is reacted with the halide of formula II (II, Y=Cl or Br) in an aprotic solvent which is a hydrocarbon such as toluene, benzene or an ether such as tetrahydrofuran, dioxane, dimethoxyethane or a mixture of two of the above solvents at a temperature between 65 °C and 110 °C.

30 8. A process for preparing (Ia) according to claim 6 where A=S, where the anion of the diphosphonate compound of formula III, formed in situ by reacting III with a base such as n-butyl lithium, is reacted with a disulfide of formula II



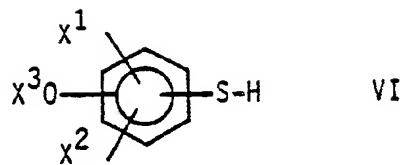
in a solvent such as tetrahydrofuran or benzene at a temperature between - 78 °C and 40 °C.

45 9. A process for preparing diphosphonic acid compounds (I) as defined in claim 1 where Z^1 = Z^2 = Z^3 = Z^4 = OH by hydrolysis of a diphosphonate ester of formula I where Z^1 = Z^2 = Z^3 = Z^4 = OEt with concentrated hydrochloric acid at reflux temperature or with bromotrimethyl silane followed by treatment of water.

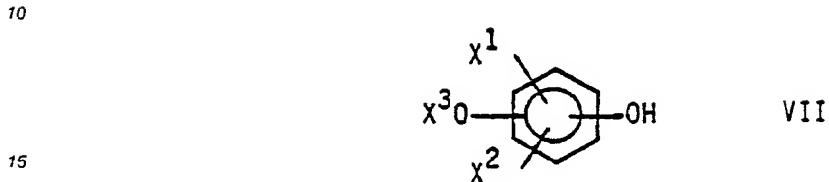
50 10. A process for preparing tetramethyl diphosphonate compounds of formula (I) as defined in claim 1, where Z^1 = Z^2 = Z^3 = Z^4 = OMe by reacting the diphosphonic acid as described in claim 9 with trimethyl orthoformate at reflux temperature.

55 11. A process for preparing cyclic esters of diphosphonates of formula (I) as defined in claim 1, where each of the two substituent pairs Z^1, Z^2 and Z^3, Z^4 forms an alkylidenedioxy ring comprising from 2 to 8 carbon atoms, which consists in reacting the diphosphonyl tetrachloride, prepared by reacting the tetraethyl ester of diphosphonate (I), where Z^1 = Z^2 = Z^3 = Z^4 = OEt sequentially with trimethylbromosilane then with phosphorus pentachloride, with a diol in presence of a tertiary amine in a polar ether solvent such as dioxane at temperature between 20 °C and 100 °C.

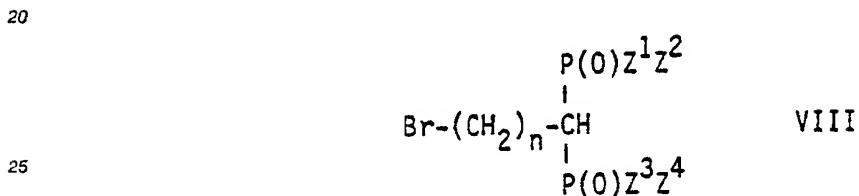
12. A process for preparing compounds (I) as defined in claim 1, where A = -S-(CH₂)_n- or -O-(CH₂)_n- which consists in reacting respectively a thiophenol of formula VI,



or a hydroquinone of formula VII

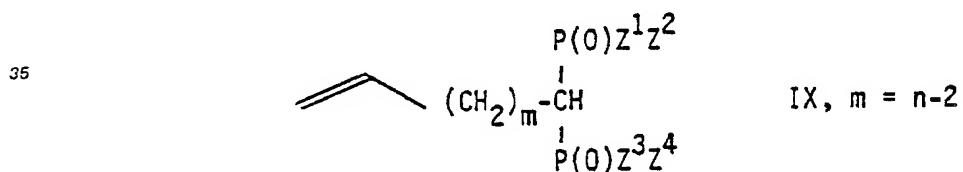


with a bromoalkylenediphosphonate of formula VIII



in presence of a base.

30 13. A process for preparing compounds (I) as defined in claim 1 where A = -S(CH₂)_n- and n ≥ 3 which involves reacting the thiophenol of formula VI and an alkenylenediphosphonate of formula IX



40 14. A process for preparing compounds of formula (I) as defined in claim 1 where A is -SO₂(CH₂)_n- which consists in oxidizing the compounds (I) where A = -S-(CH₂)_n- by using m-chloroperbenzoic acid or potassium hydrogen persulfate.

45 15. A process according to claim 1 for preparing one of the compounds of formula (I) selected from the group comprising
 tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
 tetraethyl 2-(3-tertiobutyl-4-hydroxy-5-methylphenyl)ethenylidene-1,1-diphosphonate,
 tetraisopropyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
 50 tetramethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonic acid,
 tetraethyl 2-(3,5-di-secondarybutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
 tetraisopropyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
 tetrabutyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
 55 tetraethyl 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
 tetraethyl 3,5-ditertiobutyl-4-hydroxyphenylthio-methylenediphosphonate,
 2-(3,5-ditertiobutyl-4-hydroxyphenyl)ethylidene-1,1-bis(2-oxo-1,3,2-dioxaphosphorinan) and
 2-(3,5-ditertiobutyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonic acid.

16. A process for preparing a pharmaceutical composition comprising a therapeutically effective amount of at least one diphosphonate compound of formula (I) according to claim 1 in combination with a pharmaceutically acceptable carrier.

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